Year 2000

CDC PROCEDURES FOR PROTECTION OF HUMAN RESEARCH PARTICIPANTS

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CDC Procedures for Protection of Human Research Participants

10/1/99[1]

This manual of procedures applies to all institutions engaged in research[2] involving human participants conducted by the Centers for Disease Control and Prevention (CDC)[3] or funded in whole or in part by CDC. Research, as defined by the Federal Policy for the Protection of Human Subjects (45 CFR 46) is "...a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities." This includes research conducted by CDC employees, either directly, through grants, cooperative agreements, contracts, task or purchase orders, or in collaboration with outside parties. It also includes research conducted or funded by CDC outside the United States. It also includes research conducted by grantees, cooperative agreement awardees and contractors.

A human subject (participant), according to 45 CFR 46, is defined as "...a living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information." Intervention includes both physical procedures by which data are gathered (e.g., venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. Interaction includes communication or interpersonal contact between investigator and subject. Private information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (e.g., a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.[4]

NOTE: All CDC investigators involved in research involving human participants are expected to know the contents of this manual; however, certain key areas have been highlighted. We hope these highlights help focus your attention to particular areas of

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[1] This manual will be updated annually.

[2] See the HSO intranet homepage at http://intranet.cdc.gov/od/ads/hsr2.htm for the OPRR memo defining engagement in research.

[3] References to CDC also apply to ATSDR.

[4]See the HSO intranet homepage at http://intranet.cdc.gov/od/ads/hsr2.htm for the National Center for Health Statistics confidentiality manual.

concern in research with human participants.

Office for Protection from Research Risks (OPRR) Assurance

The Office for Protection from Research Risks (OPRR), U.S. Department of Health and Human Services (DHHS), is responsible for overseeing the implementation of the Federal Regulations throughout the DHHS. CDC has provided written assurance to OPRR that it will comply with this policy codified at Title 45, Code of Federal Regulations, Part 46 (45 CFR 46). CDC's Multiple Project Assurance (MPA) (see intranet @ http://intranet.cdc.gov/od/ads/hsr2.htm) contains a detailed description of applicability, principles, CDC policy, responsibilities of CDC staff, and Institutional Review Board (IRB) structure, membership requirements, authorities and responsibilities, and procedures.

Institutional Responsibilities

Office of the Associate Director for Science (ADS)
No research activity involving human participants unless specifically exempt under 45 CFR 46 or waived by the Secretary, DHHS, shall be supported by CDC until the requirements of 45 CFR 46 have been met. The responsibility for the determination that all such requirements are met and that the rights and welfare of human participants have been and will be adequately protected resides at all levels of institutional review. However, the final determination lies with the Deputy ADS.

The Deputy ADS is the authorized individual to act on behalf of the CDC Director and ADS and assumes the obligations imposed by 45 CFR 46 regarding any research involving human participants.

Additional responsibilities of the Deputy ADS include the following:

1. Interprets 45 CFR 46 and works with IRBs, CDC researchers and Centers/Institute/Offices (CIO) to formulate and develop CDC policies and procedures consistent with the Federal Regulations.

2. Provides written procedures and guidelines for conducting research involving human participants, as needed.

3. Implements CDC's MPA.

4. Serves as the CDC liaison to OPRR.

5. Convenes regular IRB Chairs meetings. These meetings are attended by IRB Chairs, the Deputy ADS, IRB Administrators, and other interested parties.

6. Negotiates and certifies that collaborating institutions have OPRR-approved assurances and IRB approvals.

7. Appoints members to the CDC IRBs and assists CDC IRBs in carrying out their mandate.

8. Determines and documents whether research is exempt from IRB review.

9. Reviews all grant and cooperative agreement program announcements to confirm the applicability of human subjects regulations.

Human Subjects Office (HSO) (Appendix I)
Staff within the Human Subjects Office (HSO) in Atlanta are responsible for carrying out the procedures described in this manual. They include:

1. Coordination of the IRB meetings.

2. Processing of protocols, amendments, continuations and terminations.

3. Handling of expirations, suspensions, and continuations.

4. Coordination of human participants research training and educational opportunities for CDC researchers and IRB members.

5. Processing of assurances for domestic sites that do not receive funds through CDC's Procurement and Grants Office (PGO) and international sites.

At the National Institute for Occupational Safety and Health (NIOSH), responsibilities a-c are handled by the IRB Chair; at the National Center for Health Statistics (NCHS) they are handled by the IRB administrator.

Procurement and Grants Office (PGO)

1. Certifies that awardees have assurances of compliance with 45 CFR 46.

2. Certifies that awardees' protocols have initial and annual (at least) IRB review.

Centers, Institute, Offices (CIO)
Each CIO is responsible for designating a Human Subjects Contact (HSC) (see intranet @ http://intranet.cdc.gov/od/ads/hsr2.htm). The HSC:

1. Determines and documents whether activities are research or nonresearch.

2. Determines and documents whether research involves human participants.

3. Reviews and clears all protocols for IRB review.

4. Serves as the CIO expert and lead on implementing 45 CFR 46.

5. Works with the HSO, investigators, and IRB Chairs, when indicated, to resolve problems.

6. Maintains an internal system for documenting communications between the investigator and the HSO for tracking protocols.

7. For Federally-funded research:
   (a) Advises Program if human participants will be involved in proposed grant/cooperative agreement programs, contracts, task or purchase order.

(b) Advises PGO's Objective Review Group (ORG) of their responsibilities regarding review of grant/cooperative agreement applications involving human participants.

(c) Completes tracking form for grants/cooperative agreements.

(d) Completes Request for Contract, Request for Task Order, or Statement of Work for Purchase Orders check sheet to identify if project potentially involves human participants and if CDC investigators will be involved.

Investigators

Investigators are CDC staff who are working directly or in collaboration with an outside party in the design of a research study, development of methods and procedures for the study, collection of data, analysis of data, or interpretation of data. Any CDC staff who intends to become an author on a publication generated from a research study is an investigator of that research study.
Investigator's responsibilities:

1. Makes an initial determination that a proposed study is research involving human beings and that the study may need IRB review.

2. Writes or collaborates on writing the protocol and other documentation necessary for IRB review.

3. Is responsible for or collaborates with others in the conduct of the research.

4. Is responsible for keeping the IRB informed of any relevant changes to an approved protocol.

5. Is responsible for requesting continuation or termination of a protocol.

6. Is responsible for ensuring that collaborators/collaborating institutions also comply with the human subjects regulations.

Institutional Review Boards (IRBs)

CDC has six regular IRBs and one rapid assessment IRB. The regular IRBs include one at NIOSH (IRB "D"), one at NCHS, and four in Atlanta (IRBs " A, B, C and G"). The Atlanta-based IRBs review and approve research for all other CDC CIOs. CDC, Atlanta, has a rapid assessment IRB which meets on an "as needed" basis to review research that must be conducted on an emergency basis. Additional IRBs may be constituted as needed.

The primary role of the IRB is to protect the rights and welfare of human beings who are participants in the research. In accordance with the Federal Regulations (45 CFR 46.111), an IRB may approve research only after it has determined that all of the following requirements are satisfied:

1. Risks to participants are minimized: (i) by using procedures that are consistent with sound research design, and that do not unnecessarily expose participants to risks, and (ii) whenever appropriate, researchers should employ procedures that are being performed on participants for

prevention, diagnostic or treatment purposes.

2. Risks to participants are reasonable relative to anticipated benefits, if any, to participants, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

3. Selection of participants is equitable. In making this assessment the IRB must take into account the purposes of the research and the setting in which it will be conducted. The IRB must be particularly attentive to the special problems that may arise when research involves vulnerable populations, such as children, pregnant women, fetuses, prisoners, mentally disabled persons, economically or educationally disadvantaged persons. If any of the participants are likely to be susceptible to undue influence or coercion, the IRB may require additional safeguards in the study to protect such participants.

4. Informed consent will be sought from each prospective participant, or the participant's legally authorized representative.

5. Informed consent will be appropriately documented.

6. The research plan makes adequate provisions for ensuring the safety of participants.

7. There are adequate provisions to protect the privacy of participants and to maintain the confidentiality of data.

The IRB must determine if the study is minimal- or greater than minimal risk. The Federal Regulations classify research into that which is minimal or not greater than minimal risk to the participant and that which is greater than minimal risk. The definition of minimal risk given in §46.102(I) reads as follows:

"Minimal risk means that the ***probability*** and ***magnitude*** of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."

Informed Consent

The ethical principle of respect for persons (from the Belmont Report) requires that persons who participate in research shall have the opportunity to choose what shall or shall not happen to them. The IRB must judge whether three conditions are met: disclosure of information (participant has been provided full information regarding the research), comprehension (participant fully understands all ramifications of the research), and voluntariness (participant is volunteering free of coercion and undue influence).

The IRB will approve protocols that contain the following information as part of the informed consent process (45 CFR 46.116). **All of the following items must be in the consent form or waived by the IRB. If waived, a justification is required as described in 45 CFR 46.116(d) (see next page). If an item is not applicable to the research being conducted, the IRB may decide, by consensus, to waive it for you.**

1. A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the participant's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.

Note: It is CDC policy that all consent forms identify CDC as a collaborating partner when listing collaborators.

2. A description of any reasonably foreseeable risks or discomforts to the participant.

3. A description of any benefits to the participant or to others which may reasonably be expected from the research.

4. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the participant.

5. A statement describing the extent, if any, to which confidentiality of records identifying the participant will be maintained.

6. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.

7. An explanation of whom to contact for answers to pertinent questions about the research and research participants' rights, and whom to contact in the event of a research-related injury to the participant.

8. A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the participant is otherwise entitled, and the participant may discontinue participation at any time without penalty or loss of benefits to which the participant is otherwise entitled.

When appropriate, one or more of the following elements of information shall also be provided to each participant:

1. A statement that the particular treatment or procedure may involve risks to the participant (or to the embryo or fetus, if the participant is or may become pregnant) which are currently unforeseeable.

2. Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the participant's consent.

3. Any additional costs to the participant that may result from participation in the research.

4. The consequences of a participant's decision to withdraw from the research and procedures for orderly termination of participation by the subject.

5. A statement that significant new findings developed during the course of the research which may relate to the participant's willingness to continue participation will be provided to the participant.

6. The approximate number of participants involved in the study.

An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth above, or waive the requirements to obtain informed consent provided the IRB finds and documents that:

1. The research involves no more than minimal risk to the participants.

2. The waiver or alteration will not adversely affect the rights and welfare of the participants.

3. The research could not practicably be carried out without the waiver or alteration.

4. Whenever appropriate, the participants will be provided with additional pertinent information after participation.

All four criteria must be met in order to alter some or all of the consent process (45 CFR 46.116(d).

Note: It is the responsibility of the investigator to ask the IRB for a waiver of the consent process. When requesting a waiver or alteration of consent under 45 CFR 46.116(d), **a justification *must* be provided**. The IRB will not grant a waiver without written justification; rather, a requirement to include the justification will be included in the IRB's report.

The informed consent process shall be documented by the use of a written consent form approved by the IRB and signed by the participant or the participant's legally authorized representative. A copy shall be given to the person signing the form. The written consent form may be read to the participant or the participant's legally authorized representative (45 CFR 46.117), but the investigator shall give the participant or the representative adequate opportunity to read it before it is signed.

A consent form should be written at a level that is understandable to the study population. For most populations, the reading level of the consent form should be at the 8th grade level. Investigators should document to the IRB the reading level of the consent form. If the reading level is written at a different level from the 8th grade, justification should be given for the use of the reading level in the consent form.

The investigator may, as an alternative, give the participant or the representative a short written consent form which documents that the elements of the informed consent were presented orally to the participant or representative. The short written consent form is signed by the participant or representative. When this method is used, a witness should observe the oral presentation and a written summary of what is to be said to the participant or representative should be used. The witness should sign the short written consent form and the summary. The person actually obtaining consent should sign the summary. A copy of the summary should be given to the participant or the representative, in addition to a copy of the short written consent form.

An IRB may waive the requirement for the investigator to obtain a signed consent form (45 CFR 46.117 (c)) for some or all participants under one of two conditions:

1. The only record linking the participant and the research would be the consent form and the principal risk would be potential harm resulting from a breach of confidentiality. Each participant will be asked whether the participant wants documentation linking the participant with the research, and the participant's wishes will govern.

2. That the research presents no more than minimal risk of harm to participants and involves no procedures for which written consent is normally required outside the research context. In either case, the IRB may require the investigator to provide participants with a written statement regarding the research.

Note: **It is the responsibility of the investigator to ask the IRB for a waiver of DOCUMENTATION of consent.** When requesting a waiver of written documentation of consent under 45 CFR 46.117, **a justification *must* be provided**. The IRB will not grant a waiver without written justification; rather, a requirement to include the justification will be included in the IRB's report.

The IRBs recognize that the Federal Regulations were written for clinical trials and in our effort to make sections 116 (d) and 117 fit public health research (see intranet @ http://intranet.cdc.gov/od/ads/hsr2.htm) we have developed standard language for use by IRB Primary Reviewers. Three examples can be found in **Appendix II**.

Special Populations

Inclusion of Women and Minorities

The 1996 CDC policy entitled "Inclusion of Women and Ethnic Minorities in Research" requires that CDC IRBs ensure that women and racial and ethnic minority populations are appropriately represented in research. Women and members of racial and ethnic minority groups should be adequately represented in all CDC research involving human participants, unless a clear and compelling rationale and justification are given that inclusion is inappropriate or clearly not feasible. Although this policy does not apply to studies when the investigator cannot control the race, ethnicity, and gender of participants, women and racial and ethnic minority populations must not be routinely and/or arbitrarily excluded from such investigations.

In addition, women of childbearing potential should also not be routinely and/or arbitrarily excluded from participation even though there are ethical/risk issues to consider for inclusion and exclusion. Information on differences in adverse outcomes or risk profiles for pregnant women may be reason for exclusion. Therefore, pregnancy status may need to be determined prior to enrollment for some studies and, if necessary, during an intervention to safeguard the participants' health. The IRB must determine the degree of certainty of pregnancy status necessary in a study according to the potential risk imposed on the fetus. Requiring a pregnancy test in addition to a woman's self-report of pregnancy status should be dependent upon the degree of risk to the fetus.

Inclusion of women and/or racial and ethnic minority groups in research can be addressed either by including all appropriate groups in one single study or by conducting multiple studies. In general, protocols should employ a design with gender and/or minority representation appropriate to the scientific objectives. It is not a requirement that the study design provide sufficient statistical power to answer the questions posed for men and women and racial and ethnic groups separately; however, whenever there are scientific reasons to anticipate differences between men and women and/or racial and ethnic groups with regard to the hypothesis under investigation, investigators should include an evaluation of these gender and racial/ethnic group differences in the study proposal. If adequate inclusion of one gender and/or minority group is impossible or inappropriate with respect to the purpose of the proposed study, the rationale for the study population must be well explained and justified. Similarly, if in the only study population available, there is a disproportionate representation of one gender or minority/majority group, the rationale for the study population must be well explained and justified. The cost of inclusion of women and/or racial and ethnic minority groups shall not be a permissible consideration for exclusion from a given study unless data regarding women and/or racial and ethnic minority groups have been or will be obtained through other means that provide data of comparable quality.

Research Involving Prisoners

In addition to all other IRB responsibilities, any protocol involving prisoners as research participants must also meet specific requirements as described in Subpart C of the Federal Regulations. A prisoner is defined as any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a

criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trials, or sentencing.

The specific requirements are:
With respect to the IRB, a majority of the IRB (exclusive of prisoner members) members shall have no association with the prison(s) involved, apart from their membership on the IRB and at least one member of the IRB shall be a prisoner, or a prisoner representative with appropriate background and experience to serve in that capacity. However, where a particular research project is reviewed by more than one IRB only the local IRB need have a prisoner or prisoner advocate according to OPRR policy. All of the IRBs, however, must have access to the prisoner/prisoner advocate or to the meeting minutes. Of course, all of the IRBs may have a prisoner or prisoner advocate.

In addition the IRB shall approve such research only if it meets the following requirements (45 CFR 46.305 and 45 CFR 46.306):

1. The research under review represents one of the following categories:
   (a) Study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the participants.

   (b) Study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the participants.

   (c) Research on conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on hepatitis which is much more prevalent in prisons than elsewhere; and research on social and psychological problems such as alcoholism, drug addiction and sexual assaults). Following approval by the CDC IRB, the Deputy ADS will notify OPRR who will provide, via Secretary's (of DHHS) panel, final approval for the research.

   (d) Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well being of the participant. In cases in which those studies require the assignment of prisoners to control groups which may not benefit from the research, upon approval by the CDC IRB, the Deputy ADS will notify OPRR who will provide, via Secretary's (of DHHS) panel, final approval for the research.

2. Any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired.

3. The risks involved in the research are commensurate with risks that would be accepted by nonprisoner volunteers.

4. Procedures for the selection of participants within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless the investigator provides to the IRB justification in writing for following some other procedures, control participants must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project.

5. The information is presented in language which is understandable to the participant population.

6. Adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and that each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole.

7. Where the IRB finds that there may be a need for follow-up examination or care of participants after the end of their participation, adequate provision has been made for such examination or care, taking into account the varying lengths of individual prisoners' sentences, and for informing participants of this fact.

Upon approval of the protocol by the IRB, the Deputy ADS will notify OPRR about the research, the category under which it is permitted (45 CFR 46.306) and that the duties of the IRB under 45 CFR 46.305 have been fulfilled.

Finally, any protocol involving prisoners as research participants must meet all applicable state laws.

Research Involving HIV Antibody Testing

The IRB must assess the potential risk/benefit balance of the study and assure that the consent process clearly distinguishes experimental procedures from clinical care.

When HIV antibody testing is to be performed as part of a research protocol, both the protocol and the consent form must state that the HIV testing is being performed for purposes of the study; the protocol must include a justification as to why this testing is being performed; pre- and post-test counseling of the participants by qualified personnel must be performed and the participants must be informed of their test results. The participants should be counseled as to the various risks associated with HIV testing as well as the risks associated with being HIV positive. If the person is HIV positive, the various options available for treatment should be discussed; the details of this counseling, where, when and by whom it will be done, should be included in the consent form; the protocol should discuss how the confidentiality of the HIV antibody test results will be maintained.

In 1988, the Public Health Service (PHS) issued a policy stating that research participants tested

for HIV antibody, if the testing is conducted or supported by Federal funds, must receive their results and be provided with appropriate counseling. There are three exceptions: pertaining to the individual, pertaining to the protocol design, and pertaining to foreign sites. In the first exception, where there are compelling and immediate reasons that justify not informing a particular individual that is seropositive, (e.g. an indication that an individual would attempt suicide), the particular individual need not be informed of HIV test results. When this exception is made the investigators will promptly report the exception to the local IRB and the CDC IRB without identifying the individual.

The second exception pertaining to protocol design covers circumstances in which extremely valuable knowledge might be gained from research involving participants who would be expected to refuse to learn their HIV test results. The IRB shall consider the particular circumstances of the research, the characteristics of the target research participants, and other factors, and may approve a testing procedure that would allow research participants to participate without being informed of their individual results. In proposing such an exception, the investigator must demonstrate to the satisfaction of the IRB that:

1. research participants will be informed of their risk of infection;

2. research participants will receive risk reduction counseling regardless of whether they receive their test results;

3. there is good reason to believe that a requirement for test results notification would significantly impair collection of study information that could not be obtained by other means; and

4. the risk/benefit ratio to individuals, their partners, and society will be periodically re-evaluated by the IRB so that the study might be revised or terminated if it is determined that it is no longer justifiable to allow participants to continue to participate without receiving their HIV test results.

The third exception covers protocols conducted at foreign sites. Activities should be evaluated to account for cultural norms, the health resource capabilities and official health policies of the host country. If a research protocol review is involved, the reviewing IRB must consider whether any modification to the policy is significantly justified by the risk/benefit evaluation of the research.

The CDC IRB must approve any protocol that falls into exception 2 or 3. If the IRB approves the protocol, the Deputy ADS will submit the decision to the Director, CDC. Prior to or at the same time that the decision is being posed to the Director, CDC, it must also be sent to OPRR. In the event that the Director, CDC disagrees with the IRB's decision and will not approve the exception, the IRB will be so informed. The Director, CDC could not, however, approve the exception if the IRB disapproved it.

Research Involving Pregnant Women, Fetuses, and Human *in Vitro* Fertilization

Although the Federal Regulations regarding this category of research have changed, the final revisions are not yet published; therefore, researchers involving pregnant women, fetuses, and human *in vitro* fertilization as the target of their research must still follow the regulations as specified in 45 CFR 46.

In addition to all other IRB responsibilities, for any research involving fetuses, pregnant women, and human *in vitro* fertilization, the IRB shall meet the specific requirements described in Subpart B of the Federal Regulations. Pregnancy encompasses the period of time from confirmation of implantation (through any of the presumptive signs of pregnancy, such as missed menses, or by a medically acceptable pregnancy test), until expulsion or extraction of the fetus. Fetus means the product of conception from the time of implantation until a determination is made, following expulsion or extraction of the fetus, that it is viable (being able, after either spontaneous or induced delivery), to survive (given the benefit of available medical therapy) to the point of independently maintaining heart beat and respiration). *In vitro* fertilization means any fertilization of human ova which occurs outside the body of a female, either through admixture of donor human sperm and ova or by any other means.

The CDC IRB will, in addition to the other requirements in the Federal Regulations, determine that adequate consideration has been given to the manner in which potential participants will be selected, and adequate provision has been made by the investigator for monitoring the actual informed consent process (e.g., through such mechanisms, when appropriate, as participation by the IRB or participant advocates in: (I) overseeing the actual process by which individual consents required by this Subpart are secured either by approving induction of each individual into the activity or verifying, perhaps through sampling, that approved procedures for induction of individuals into the activity are being followed, and (ii) monitoring the progress of the activity and intervening as necessary through such steps as visits to the activity site and continuing evaluation to determine if any unanticipated risks have arisen).

General Limitations Related to This Research

No activity to which this Subpart is applicable may be undertaken unless:

1. Appropriate studies on animals and nonpregnant individuals have been completed.

2. Except where the purpose of the activity is to meet the health needs of the mother or the particular fetus, the risk to the fetus is minimal and, in all cases, is the least possible risk for achieving the objectives of the activity.

3. Individuals engaged in the activity will have no part in any decisions as to the timing, method, and procedures used to terminate the pregnancy, and determining the viability of the fetus at the termination of the pregnancy.

4. No procedural changes which may cause greater than minimal risk to the fetus or the pregnant woman will be introduced into the procedure for terminating the pregnancy solely in the interest of the activity.

No inducements, monetary or otherwise, may be offered to terminate pregnancy for purposes of the activity.

Activities Directed Toward Pregnant Women

No pregnant woman may be involved as a participant in an activity covered by this Subpart unless:

1. The purpose of the activity is to meet the health needs of the mother and the fetus will be placed at risk only to the minimum extent necessary to meet such needs, or

2. The risk to the fetus is minimal. Any research protocol permitted under this Subpart may be conducted only if the following requirements are met: the mother and father are legally competent and have given their informed consent, except that the father's informed consent need not be secured if: the purpose of the activity is to meet the health needs of the mother, his identity or whereabouts cannot reasonably be ascertained, he is not reasonably available, or the pregnancy resulted from rape.

Activities Directed Toward Fetuses in Utero

No fetus *in utero* may be involved as a participant in any activity covered by this Subpart unless:

1. The purpose of the activity is to meet the health needs of the particular fetus and the fetus will be placed at risk only to the minimum extent necessary to meet such needs, or

2. The risk to the fetus imposed by the research is minimal and the purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means.

Any research protocol permitted under this Subpart may be conducted only if the following requirements are met: the mother and father are legally competent and have given their informed consent, except that the father's informed consent need not be secured if his identity or whereabouts cannot reasonably be ascertained, he is not reasonably available, or the pregnancy resulted from rape.

Activities Directed Toward Fetuses ex Utero, Including Nonviable Fetuses

Until it has been ascertained whether a fetus *ex utero* is viable, a fetus *ex utero* may not be involved as a participant in an activity covered by this Subpart unless:

1. There will be no added risk to the fetus resulting from the activity, and the purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means, or

2. The purpose of the activity is to enhance the possibility of survival of the particular fetus to the point of viability.

No nonviable fetus may be involved as a participant in an activity covered by this Subpart unless:

1. Vital functions of the fetus will not be artificially maintained,

2. Experimental activities which of themselves would terminate the heartbeat or respiration of the fetus will not be employed, and

3. The purpose of the activity is the development of important biomedical knowledge which cannot be obtained by other means.

In the event the fetus *ex utero* is found to be viable, it may be included as a participant in the activity only to the extent permitted by and in accordance with the requirements of other parts of the Federal Regulations.

Any protocol involving pregnant women, fetuses, and *in vitro* fertilization as research participants must meet all applicable state laws. Activities involving the dead fetus, macerated fetal material, or cells, tissue, or organs excised from a dead fetus shall be conducted only in accordance with any applicable state or local laws regarding such activities.

Waivers to these requirements may be granted only after approval by the IRB and the Secretary, DHHS.

Research Involving Children

In addition to all other IRB responsibilities, any protocol involving children must meet specific requirements as described in Subpart D of the Federal Regulations. Children are persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted (46.402(a)). This definition, when read in the context of the Federal Regulations requires a review of state or local law to determine the age at which an individual can consent to participation in research without parental permission. 46.402(a) should be interpreted in conjunction with each state's laws related to age of majority, emancipation and other relevant laws. The mere existence of laws authorizing minors to consent to specific medical treatments (e.g. treatment of sexually transmitted diseases) should not be broadly interpreted to authorize minors to consent to research regarding that treatment, unless so stated in the law. This interpretation should not unduly restrict otherwise ethical research. IRBs may waive the requirement for parental permission in accordance with the procedures set forth in 46.116 or 46.408(c) if appropriate measures are taken to protect the interests of minors.

The IRB must consider the benefits, risks, and discomforts of the research and assess their justification for children's participation in light of the benefits to the child-participant(s) or to society as a whole. In calculating the risks and benefits, the IRB should consider the circumstances of the participants under study, the magnitude of risks or discomforts that may accrue from research participation and the potential benefits the research may provide to the participant or class of participants.

An important aspect of IRBs' considerations of research involving children is an evaluation of what constitutes "minimal risk." Procedures which generally present no more than minimal risk to healthy children include: urinalyses, small amounts of blood obtained by venipuncture, electroencephalography (EEG), allergy scratch tests, minor changes in diet or daily routine, and/or the use of standard psychological or educational tests. However, the assessment of the probability

and magnitude of harm or discomfort may be different in ill children and may vary depending on the diseases or conditions that the children may have. For example, obtaining research blood samples from a very ill and anemic child may present more than minimal risk to the child. The IRB must also consider the extent to which research procedures would be a burden to a child-participant, regardless of whether the child is accustomed to the proposed procedures. Procedures that exceed minimal risk may be difficult to define in the abstract, but should not be difficult to identify on a case-by-case basis. Higher risk procedures might include biopsy of internal organs, spinal taps, or the use of drugs whose risks to children have not yet been established. Behavioral interventions likely to cause psychological stress also may exceed minimal risk.

Additionally, for any research involving children the IRB must verify that the research protocol has made adequate provisions for soliciting the assent of the children and the permission of the parents or legal guardian. Assent means a child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent. Permission means the agreement of parent(s) or guardian to the participation of their child or ward in research. Parent means a child's biological or adoptive parent. Guardian means an individual who is authorized under applicable state or local law to consent on behalf of a child to general medical care.

When children are involved in research, the IRB must make provisions for the assent of the children and the permission of the parents. The IRB must determine whether the permission of both parents is required.

Although children are not capable of giving legally valid consent, they may be able to assent or dissent from participation. Out of respect for children as developing persons, they should be asked whether they wish to participate in research, particularly if they can comprehend and appreciate what it means to be a volunteer for the benefit of others and the research is not likely to benefit them directly. Taking into account such factors as the nature of the research, and the age, status and medical condition of potential participants, the IRB must determine for each protocol, whether all or some of the children are capable of assenting to participation. There is no requirement that assent be sought at a specific age, but that it be sought when in the judgment of the IRB, the children are capable of providing assent. Generally, CDC IRBs require that assent be obtained from children seven years of age and older.

If the IRB determines that the capability of some or all of the children is so limited that they cannot reasonably be consulted or that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research, the assent of the children is not a necessary condition for proceeding with the research. Even where the IRB determines that the participants are capable of assenting, the IRB may still waive the assent requirement under the criteria for waiving consent in 45 CFR 46.116.

In addition to the criteria for waiving consent in 45 CFR 46.116, if the IRB determines that a

research protocol is designed for conditions or for a participant population for which parental or guardian permission is not a reasonable requirement to protect the participants (for example, neglected or abused children), it may waive the usual consent requirements, provided an appropriate mechanism for protecting the children who will participate in the research is substituted, and provided further that the waiver is consistent with Federal, state, and local laws. The choice of an appropriate mechanism would depend upon the nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the research participants, and their age, maturity, status, and condition.

Wards of the State

Children who are wards of the state or any other agency, institution, or entity can be included in research only if such research is:

1. related to their status as wards; or

2. conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as participants are not wards.

The IRB shall require appointment of an advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as guardian or in loco parentis. One individual may serve as advocate for more than one child. The advocate shall be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child's participation in the research and who is not associated in any way (except in the role as advocate or member of the IRB) with the research, the investigator(s), or the guardian organization.

Categories for Research Involving Children

The IRB must classify the research into one of four categories and must document in the minutes their discussions of the risk and benefits of the research study. The IRB may approve research in each of these four categories of research involving children:

1. Research that does not involve greater than minimal risk to children.

   The IRB may approve research in this category if adequate provisions are made for obtaining assent of the children and the permission of their parents or guardian. The IRB may decide that the permission of one parent is sufficient for the research to be conducted.

2. Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual (child) participant.

   To approve research in this category, the IRB must determine that the risk is justified by the anticipated benefit to the participants, the relation of the anticipated benefits to the risk is at least as favorable to the participants as that presented by available alternative approaches, and adequate provision is made for obtaining assent of the children and permission of their parents or guardian. The IRB may decide that the permission of one parent is sufficient for the research to be conducted.

3. Research involving greater than minimal risk and no prospect of benefit to the individual (child) participant, but likely to yield generalizable knowledge about the participant's disorder or condition.

   To approve this category of research, the IRB must first determine that the risk of the research represents no more than a minor increase over minimal risk; that the intervention or procedure presents experiences to the child-participants that are reasonably commensurate with those inherent in their actual, or expected medical, dental, psychological, social, or educational situations; the intervention or procedure is likely to yield generalizable knowledge about the participant's disorder or condition which is of vital importance for understanding or amelioration of the disorder or condition; and adequate provisions are made for obtaining assent of the children and permission of their parents or guardian. The permission of both parents must be obtained unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

4. Research not otherwise approvable under one of the other three categories but the IRB determines that the study presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children.

   In these cases upon approval by the CDC IRB, the Deputy ADS will notify OPRR who will provide final approval for the research.

Any protocol involving children as research participants must meet all applicable state laws.

Research Involving CDC Employees

Occasionally, there may be circumstances under which an investigator wishes to use CDC employees as research participants.

The protocol must contain the procedures that will be used to assure that participation is voluntary and there is no coercion by supervisors, peers or other groups. To help in this, the investigator must consider obtaining volunteers from units outside the investigator's and his/her supervisor's unit or posting an announcement about the research project and the need for volunteers. The announcement must be included in the protocol. Regardless of what mechanism is used, the consent form must include a provision that emphasizes strongly that the individual's participation is truly voluntary, and the fact that the individual can contact the HSO (Atlanta), the Chair of the IRB (NIOSH) or the IRB Administrator (NCHS) to file complaints about possible coercion.

For each protocol that uses CDC employees as research participants, a list of individuals who have participated must be maintained and supplied to the IRB, in case there is a need by the IRB to interview the participants for an investigation of alleged coercion.

The consent form and the protocol must contain all of the conditions under which the CDC employee will participate.

The protocol must contain the procedures utilized to assure that sensitive data remain confidential. The best solution is to have no demographic data collected.

If demographic data are collected, or results are provided to the participant, procedures must be described to minimize the risk of an individual's co-workers identifying participants. One solution might be to have a third party (outside of CDC) collect the data. This third party would then have the only "cross-file" that would link results with an individual.

The protocol and consent form must contain a statement as to the expected number and duration of time that CDC employees will be expected to spend in the study and whether compensation will be offered. The consent form must appropriately cover the liability issues if the individual participates on his/her own time or during his/her regular tour of duty.

Research Involving Non-English Speaking Participants

The IRB should assure that adequate provisions have been made for appropriate translation of the consent document or the availability of translators to ensure an adequate understanding of the research project. **Although back translations of consent documents are not required in the Federal Regulations, CDC policy requires an investigator to provide a translation and back translation of the consent document in order to approve the protocol. Both documents must be submitted with the protocol.**

Research participants who do not speak English should be presented with a consent document written in a language understandable to them. When written documentation is not feasible, oral presentation of informed consent information in conjunction with a short written consent document (stating that the elements of consent have been presented orally) and a written summary of what is presented orally may be used. A witness to the oral presentation is required, and the participant must be given copies of the short written consent document and the summary. When this procedure is used with participants who do not speak English, the oral presentation and the short written consent document should be in a language understandable to the participant; the IRB-approved English language informed consent may serve as the summary; and the witness should be fluent in both English and the language of the participant.

Research Involving Food and Drug Administration (FDA) Regulated Test Articles

Any research study involving FDA regulated test articles must meet the requirements of 45 CFR 46 and FDA regulations for protecting human subjects, 21 CFR 50 and 21 CFR 56. A test article means any drug for human use, biological product for human use, medical device for human use, human food additive, color additive, electronic product or any other article subject to regulation by the Food, Drug and Cosmetic Act or under sections 351 or 354 of the PHS Act.

The definition of a "device" includes i*n vitro* diagnostic products devices that aid in the diagnosis of disease or medical/physiological conditions (e.g., pregnancy) by using human or animal components to cause chemical reactions, fermentation, and the like. A few diagnostic products are intended for use in controlling other regulated products (such as those used to screen the blood supply for transfusion-transmitted diseases) and are regulated as biological products.

Institutional Review Boards

Establishment and Composition of CDC's IRBs
Each IRB must be sufficiently qualified through the experience and expertise of its members, and the diversity of the members' background, to foster respect for its advice and counsel in safeguarding the rights and welfare of human participants. In addition to possessing the professional competence necessary to review and approve specific research activities, the IRB must be able to ascertain the acceptability of proposed research in light of:

1. ethical principles set forth in the Belmont Report;

2. the Federal Regulations, 45 CFR 46;

3. applicable Federal, state, and local laws; and

4. standards of professional conduct and practice.

IRB members and Chairs are appointed by the CDC Deputy ADS for two-year renewable terms, after having been nominated by their CIO HSC. Each CDC IRB shall have a Chair, co-Chair, and at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. Each IRB shall have two people who are not affiliated with CDC and at least one person who is a nonscientist. Major scientific disciplines such as medicine, laboratory sciences, epidemiology, and behavioral and social sciences must be represented on each IRB. Each IRB shall have at least one female member and a proportion of membership representing minorities appropriate to the types of research reviewed.

An IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of complex issues which require expertise beyond or in addition to that available on the IRB. These individuals become *ad hoc* members and will not vote with the IRB. Changes in IRB membership are reported to OPRR.

Rapid Assessment Board
This IRB reviews emergency research which is defined generally as research resulting from the sudden onset of a public health threat that requires an immediate response by CDC investigators. Generally, CDC conducts approximately one to two emergency research studies annually. This IRB consists of five people, including one person not affiliated with CDC, and one nonscientist. Three, with at least one being a nonscientist, in attendance constitutes a quorum.

Conflict of Interest
No IRB may have a member participating in the IRB's initial or continuing review of any protocol in which the member has a conflicting interest, except to provide information requested by the IRB. A conflicting interest is defined as any interest in the research such that a member might not be able to review objectively a protocol for protection of human participants according to the Federal Regulations. Types of interests that may cause a conflict are financial interest, special or

unusual knowledge about the research, direct involvement in the research, supervision of any of the research investigators by the member, supervision of the member by the research investigators or personal involvement with the investigators. In addition, any time an IRB member feels uncomfortable about participating in the review of a protocol, that member may have a conflict of interest.

Each IRB member is required to sign a conflict of interest form at the beginning of each IRB meeting stating whether he/she has a conflicting interest with any item on the agenda. These forms are collected and maintained by the Program Specialist (Atlanta), the IRB Administrator (NCHS), or the IRB Chair (NIOSH). During the discussion of the agenda item which is of conflict to the member, the member must leave the room and recuse himself or herself from the discussion and vote on the issue. A quorum of remaining IRB members is required for full board deliberation of the agenda item.

IRB Meetings

The IRBs convene once a month at a specific CDC facility. . Additional meetings for the NCHS and NIOSH IRBs are called as needed.

In Atlanta, the Human Subjects Manager (HSM) in consultation with the IRB Chairs, is responsible for setting the agenda for each meeting and calling convened meetings as often as required to accomplish the business of the IRB. The HSM places the protocol on the agenda for a designated IRB meeting. The Program Specialist prepares an agenda packet which includes each new protocol, amendment or continuation being reviewed. In addition to the protocols, the packet also includes appropriate checklists (**Appendix IV**), the Absence of Conflict of Interest form and a list of items that were expedited during the period between meetings. At least seven days before the IRB meeting, the packet is sent to each member of the IRB. At NCHS, the IRB Administrator performs these functions. At NIOSH, the IRB Chair sets the agenda, convenes each meeting and handles the Absence of Conflict of Interest form; the investigator sends the protocol to the Chair and each member of the IRB.

Meetings are generally closed to non-IRB members. However, investigators may attend to clarify issues at the request of the IRB. Deliberations and voting on protocols is closed. Full board actions require the presence of a quorum of the voting members, defined as a 50% plus one majority of the membership including at least one member who is a nonscientist. If any member recuses himself or herself because of a conflict of interest, a quorum of the remaining members is needed for full board actions.

A primary reviewer (PR) system is used to review new protocols, amendments, and requests for continuations. The HSM, or the IRB Administrator, in consultation with the IRB Chairs, assigns a new protocol, amendment, or request for continuation to an IRB member for primary review. All IRB members are expected to review all items on the agenda. For new protocols, the PR is responsible for making a presentation describing the research, including any important human participants protection issues. The PR drafts the IRB report, which the Chair ~~also~~ reviews. The IRB Chair is ultimately responsible for the IRB report that is sent to the investigator. For

amendments and requests for continuation, the PR is responsible for reviewing the protocol folder in its entirety, and for making a presentation describing the requested change (if an amendment is requested) or describing progress on the study (if it is a request for continuation).

Note: PRs are encouraged to contact investigators (except NCID investigators) prior to the IRB meeting at which his/her protocol will be discussed in order to resolve any questions regarding the protocol. This can be an efficient way to get information and resolve issues that may be likely to surface during the IRB meeting. While CIOs other than NCID allow IRB members to contact investigators directly, it is important for all to remember to document any direct interactions with CDC investigators by ccing the appropriate CIO human subjects contact and the HSO (through the Human Subjects Review-OD mailbox). Also, please cc the CIO human subjects contact and the HSO on emails summarizing the results of phone conversations with investigators. If additional information is requested/given, the PR should request that it be given in writing (e.g., email) so that it can be added to the IRB record.

IRB meetings are conducted in accordance with Robert's Rules of Order. That is, at a minimum, the Chair conducts the meetings from a predetermined agenda and the minutes of the prior meeting are voted upon. All actions and resolutions require a voice or show-of-hands vote of the members present following discussion and the making and seconding of a motion. Minutes from every meeting must include the recording of attendees; any actions taken; the vote on the actions, including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controversial issues. Also included are the resolution and documentation of special requirements for research involving prisoners (Subpart C) and children (Subpart D). The Program Specialist is responsible for taking minutes for the Atlanta-based and NCHS Boards; at NIOSH, it is handled by the IRB Chair.

OPRR does not allow the use of conference calls for IRB meetings; however, teleconferencing (e.g., ENVISION may be used).

IRB Actions on Research Protocols

An IRB may vote to approve, to approve upon receipt of satisfactory responses to specific issues, to defer action, or to disapprove a protocol action. If a protocol action is reviewed through the expedited review process as outlined in 45 CFR 46.110, the designated primary reviewer may not defer action or disapprove a protocol; deferral of action of disapproval requires a full Board vote. A Board may defer action on a protocol if it determines that substantive modifications or clarifications are needed before it can even conduct a comprehensive review of the protocol. A Board may vote to disapprove a protocol if it determines that the basic criteria for IRB approval of research as outlined in 45 CFR 46.111 have not been met. At this point, if the Board has voted to approve a protocol upon receipt of satisfactory responses, the Board decides whether the investigator's response to the IRB report comes back to the full Board for review or may be reviewed by the primary reviewer in consultation with the Chair. If the full Board votes to defer action or to disapprove a protocol, it must go back to the full Board for reconsideration.

These actions require the vote of a majority of the members present at the meeting. The Chair does not vote, except to break a tie. If the vote is not unanimous, the minority opinion may be incorporated into the minutes of the meeting or attached to the minutes. A member may abstain from voting for any reason, without explanation. A member may also change his/her vote up until the time the vote is announced by the Chair, after which time a member's vote may be changed only with the permission of the IRB and may be granted by general consensus.

After the IRB reviews a protocol action, either through the expedited review process or at a meeting of the full Board, the Chair and/or primary reviewer will either notify the Human Subjects Office that an approval may be issued or will write a report to investigators detailing the IRB action taken, i.e., approved pending receipt of satisfactory responses to the issues outlined in the report; action deferred, with an explanation as to why and what issues need to be addressed before the Board can reconsider the protocol; or disapproved with an explanation as to why and what substantive modifications will need to be made to the protocol before it may be resubmitted for IRB review, if investigators desire to do so.

An IRB report is written by the primary reviewer to the CDC investigator and outlines the issues and concerns of the IRB. The first section of the report, General Comments and IRB Actions, tells the investigator exactly what action was taken by the IRB. The remainder of the report is divided into three categories that address (1) protocol issues, (2) consent form issues, and (3) addenda issues (scripts, questionnaires, brochures, etc.). These categories are further subdivided as follows:

Response Required, Action Required. These are issues for which the IRB requires (in accordance with the federal regulations) that investigators provide a written response and that they make the necessary revisions to the protocol, consent form, or other related documents before the protocol can be approved. If necessary, the IRB will include an explanation as to how the requested changes relate to the protection of human subjects, provide guidance, and/or provide examples of suggested revisions. If the required action cannot be carried out or investigators do not wish to make the suggested changes, investigators must submit an acceptable explanation and/or justification in their response to the IRB.

Response Required, Action Optional. These are issues for which the IRB requires that investigators provide a written response, but for which approval is not contingent upon investigators accepting the suggested changes. Investigators' responses should, however, indicate to the IRB that they have considered the scientific and ethical impact and consequences of the issues.

Of Note (for information only; no response or action required). These issues include minor comments, notes of grammatical or typographical errors, etc. Although the IRB is not requiring any response or action on the part of the investigators, these are issues that if clarified may improve the IRB's understanding of the study's purpose and/or design or may clarify issues to the participants.

In Atlanta, the IRB Chair or his/her designee forwards the IRB report to the IRB Reports - OD electronic mailbox. The Human Subjects Manager or Program Specialist (Atlanta) or the IRB Chair (NCHS and NIOSH) forwards via registered e-mail or via interoffice hardcopy the IRB report to the investigator. The investigator then submits a written response to the IRB report to the Human Subjects Review - OD electronic mailbox (Atlanta) or electronically to the IRB Chair (NCHS and NIOSH), or may forward three hardcopies of the response to the Human Subjects Specialist (Atlanta) or the IRB Chair (NCHS and NIOSH). If the IRB had previously determined that the response would be reviewed by the Chair and primary reviewer, the Human Subjects Office will forward the investigator's response for their review. If the Board had decided that the response would be reviewed by the full Board, review of the response is placed on the agenda for the full Board's next meeting.

When the Chair or his/her designee determines that the investigator's response is satisfactory and notifies the Human Subjects Office that the protocol has been approved, and after any assurance issues have been resolved and the investigator has submitted clean copies of the revised protocol, consent form, or related documents for the official file, an approval memorandum is issued to the investigator by the Human Subjects Office.

Appendix III includes an example of the IRB report format and guidelines for interpreting and responding to IRB reports.

Appeal of IRB Actions

By Federal regulation, institutional officials may not approve research that has been disapproved by an IRB. There is no mechanism for an appeal of IRB decisions to other institutional components; the IRB is an autonomous entity with its decisions being binding. Investigators may request an IRB to reconsider a decision regarding a research protocol. However, investigators do not have the option to seek the reversal of an IRB decision by submitting the same protocol to another CDC IRB.

Reporting of Adverse Events (AE) and Breaches in Protocol (Appendix V)

Any adverse event (AE) including physical, psychological, and social injuries to participants and unanticipated problems that are reported to an IND sponsor must be reported to the IRB. Serious events should be reported within 24 hours to the IRB; other events should be reported within two weeks. The report should include a statement about the nature of the AE, impact on participants, and what has been done to correct the problem. Following review by the IRB, the IRB Chair will notify the Deputy ADS.

Breaches in protocol and unanticipated problems must be reported to the IRB within two weeks of their occurrence. Breaches in protocol and unanticipated problems include, but are not limited to, breakdowns in the consent process, violations of confidentiality of the data, and complaints by participants. A report should include a statement about the nature of the breach or problem, impact on participants, and what has been done to correct the problem. Following review by the IRB, the IRB Chair will notify the Deputy ADS, who will notify OPRR in writing of the incident and the corrective actions taken.

IRB Records Management

The HSO (Atlanta), the IRB Administrator (NCHS) or the IRB Chair (NIOSH) maintains copies of protocols and consent documents that each IRB has reviewed including continuing reviews; scientific evaluations, if any, that accompany protocols; minutes of its meetings; a current approved membership list; progress reports submitted by investigators; reports of injuries to participants; copies of all correspondence between the IRB and investigators; statements of significant new findings provided to participants; and documentation of collaborative and cooperative research activities occurring at other institutions with other OPRR-approved assurances, including documentation of protocol and consent form approval by the IRBs at these sites. All records and documents are maintained for at least three years after completion of the research, and the records are accessible for inspection and copying by authorized representatives of OPRR.

Protocol Handling
(Appendix VI - Forms)

New Protocols

All research studies, including pilot studies, involving CDC investigators must be reviewed and approved by a CDC IRB before they begin, unless they are exempt from IRB review. Investigators develop and write or collaborate on the development and writing of research protocols for submission to the IRB. (**Note**: If the research is collaborative, the same protocol should be submitted to each involved IRB.) The protocol is reviewed and cleared at the CIO level (division level -- NIOSH) of CDC. Final clearance at this level is given by the designated human subjects research official for the CIO. The protocol, with CDC form 0.1250, *Request for New Protocol Approval,* and other required forms, is consecutively numbered and sent electronically to the HSO (Atlanta), IRB Administrator (NCHS), or the IRB Chair (NIOSH) who logs it into a protocol database. At NIOSH, for any protocol requiring regular, full-board review, the investigator sends a copy of the protocol to each NIOSH IRB member. A file is created and maintained for every protocol. The file contains the protocol and every accompanying form issued during the life of the protocol. The HSM (Atlanta), IRB Administrator (NCHS), or the IRB Chair (NIOSH) reviews and determines, based upon 45 CFR 46.110, whether the protocol is eligible for review by the expedited review process or whether it requires full board review. Each new research protocol is assigned to an IRB in order of readiness.

The HSO continues to receive new protocols for existing research. When submitting this type of research, please clearly identify it as existing research and include a status report.

For funded research, if PGO has restricted funding pending CDC IRB approval, please so indicate in a memo or on the CDC 0.1250 form. This information will help the HSO and IRB to act as quickly as possible in the processing and review of the protocol.

Amendments

In conducting the research study, if changes to the protocol, consent form, or other study documents are needed from what was approved by the IRB, the investigator electronically submits a description of and justification for the change in the protocol, along with CDC form 0.1252, *Request for Amendment*, to the IRB through the HSO (Atlanta), the IRB administrator (NCHS) or the IRB Chair (NIOSH). If it is a minor amendment (e.g., additional sites added, submission of site specific consent forms, revisions of data collection documents that do not add increased sensitivity to the originally approved protocol, expansion of the study population that does not include inclusion of new categories of participants, addition/deletion of laboratory tests that do not increase the risk or impact the validity of the study) which presents no additional risks to the participant, the review and approval are handled by the expedited review process. Anything other than a minor amendment must go to the full IRB for approval.

If significant findings are reported in the literature that may result in a change in the risks or benefits associated with the study or require a change in the protocol, the investigator should

report the literature findings to the IRB immediately along with recommended corrective actions to the protocol for approval.

Continuation of Protocol Approvals

A research protocol must be reviewed by an IRB until the study is completed. Completion of a study is defined as completion of data analysis or removal of identifying information from the data. Approval for a research protocol is valid for no more than one year. IRBs are required by the Federal Regulations to conduct continuing reviews of research at intervals appropriate to the degree of risk, but not less than once a year. The investigator is responsible for the timely submission of a continuing review application to the IRB that previously reviewed the protocol. Research protocols that required full IRB review initially and that have not completed participant accrual generally require full IRB review for continuation; the review must take place at a convened meeting of the IRB and must be approved by a majority of the members present. The IRB's stipulations, if any, must be met by the investigator before approval for continuation is granted. At the time of continuation reapproval, research protocols that required full IRB review initially, have completed participant accrual, and are in the process of analyzing data, may be reviewed using the expedited process. Research protocols that were reviewed using the expedited review process initially may be reviewed using the expedited review process as long as the degree of risk associated with the study has not changed.

To assist investigators in submitting continuation requests in a timely fashion, 90 days before protocol expiration, the PS (Atlanta), the IRB Administrator (NCHS) or the IRB Chair (NIOSH) notifies, via registered E-mail, the investigator of the upcoming deadline. The investigator is asked to submit electronically a *Request for Approval of Continuation of Protocol Approval*, CDC form 0.1251. A second notice is sent 60 days before expiration, if the investigator has not responded. If necessary, 30 days before expiration, the Deputy ADS, submits, via registered E-mail to the CIO HSC, a request for the status on the protocol and for the investigator to complete the form. Requests for continuation must be received by the HSO 45 days prior to the expiration date. The HSO cannot guarantee that requests for continuation submitted fewer than 45 days prior to the expiration date will be processed and reapproved prior to the expiration date.

A continuation request must include all of the following:

1. request for protocol continuation form (CDC form 0.1251)

2. copy of the currently approved informed consent document if participants are being accrued

If changes in the protocol are substantive or there are changes in the consent document, data collection instruments or site locations, an amendment request (CDC form 0.1252) should be submitted along with the continuation request, CDC form 0.1251.

If the continuation request is not received by the protocol’s expiration date, the IRB will terminate the approval of the protocol. A termination letter is sent to the HSC and the investigator with a copy to OPRR. Reactivation of the study requires submission of a new protocol to the IRB.

If the continuation request is received prior to the expiration date, but the IRB approval of the protocol expires before it is reapproved, the investigator and HSC are notified that no new participants can be accrued until the protocol is approved by the IRB. If the continuing review is under active consideration by the IRB, but has not been approved one month after the expiration due, the investigator will be notified again that participant accrual is suspended and that unless the continuing review process is completed within 45 days from the date of this final reminder, all protocol activities may be suspended or terminated.

The timing of submission of the continuation request does not affect the anniversary date for subsequent reviews, i.e., there is no "resetting the clock" for the next due date, unless the IRB requires an earlier review. Approval dates are set to the anniversary date of the initial IRB approval of the protocol.

For all actions taken by the IRB on new, continuing, or amended protocols that result in ANY changes to the protocol, consent form(s) and/or other ancillary documents, a "marked up" and a final "CLEAN" copy of these documents is required in the HSO before final IRB approval is given. A "marked-up" copy is one that shows, by "strike-out" or "redlining," those changes that were made. A "CLEAN" copy is defined as one that has the changes incorporated but for which the "strike-outs" and "relines" have been removed.

Terminations

As mentioned previously, a protocol must be reviewed by an IRB until the study is completed. Completion of a study is defined as completion of data analysis or removal of identifying information from the data. Once the study is completed, a termination notice should be submitted to the HSO through the CIO HSC.

To assist investigators in submitting termination notices, CDC form 0.1253, *Request for Termination of Protocol*, has been developed. The investigator is asked to submit this form at the completion of the study in order to formally notify the IRB of the termination and for the HSO to formally retire the protocol.

The same procedure should be used for studies that were canceled (never started) after submission to the HSO.

Expedited Review

The HS Manager (Atlanta), IRB administrator (NCHS), or the IRB Chair (NIOSH) determines whether a new protocol, amendment, or continuation request is eligible for expedited review. Under an expedited review procedure, the review is carried out by the IRB Chair or the Chair's designee. In reviewing the research, the reviewers may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. A research activity may be disapproved only after it is reviewed in accordance with the nonexpedited procedure set forth in 45 CFR 46.108(b). At every IRB meeting, each member is provided with a written report of any protocols handled through expedited review since the last regular meeting.

Applicability

1. Research activities that (1) present no more than minimal risk to human subjects, and (2) involve only procedures listed in one or more of the following categories, may be reviewed by the IRB through the expedited review procedure authorized by 45 CFR 46.110 and 21 CFR 56.110. The activities listed should not be deemed to be of minimal risk simply because they are included on this list. Inclusion on this list merely means that the activity is eligible for review through the expedited review procedure when the specific circumstances of the proposed research involve no more than minimal risk to human subjects.

2. The categories in this list apply regardless of the age of subjects, except as noted.

3. The expedited review procedure may not be used where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal.

4. The expedited review procedure may not be used for classified research involving human subjects.

5. IRBs are reminded that the standard requirements for informed consent (or its waiver, alteration, or exception) apply regardless of the type of review--expedited or convened--utilized by the IRB.

Selected categories of research may be reviewed through an expedited review procedure, if the research involves no more than minimal risk as specified in the Federal Regulations. These categories include (categories one (1) through seven (7) pertain to both initial and continuing IRB review):

1. Clinical studies of drugs and medical devices only when condition (a) or (b) is met.
   (a) Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)

   (b) Research on medical devices for which (i) an investigational device exemption application (21 CFR Part 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

2. Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:
   (a) from healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or

(a) from other adults and children[5] considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.

3. Prospective collection of biological specimens for research purposes by noninvasive means. Examples:
   (a) Hair and nail clippings in a nondisfiguring manner;

   (b) deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction;

   (c) permanent teeth if routine patient care indicates a need for extraction;

   (d) excreta and external secretions (including sweat);

   (e) uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue;

   (f) placenta removed at delivery;

   (g) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor;

   (h) supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques;

   (i) mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings;

   (j) sputum collected after saline mist nebulization.

4. Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.)

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[5] Children are defined in the HHS regulations as “persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted." 45 CFR 46.402(a).

Examples:

(a) Physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy;

(b) weighing or testing sensory acuity;

(c) magnetic resonance imaging;

(d) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography;

(e) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

5. Research involving materials (data, documents, records, or specimens) that have been collected or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis). (Note: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.101(b)(4). This listing refers only to research that is not exempt.)

6. Collection of data from voice, video, digital, or image recordings made for research purposes.

7. Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. (Note: Some research in this category may be exempt from the HHS regulations for the protection of human subjects 45 CFR 46.101 (b)(2) and (b)(3). This listing refers only to research that is not exempt.)

8. Continuing review of research previously approved by the convened IRB as follows:
   (a) Where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects; or

   (b) Where no subjects have been enrolled and no additional risks have been identified; or

   (c) Where the remaining research activities are limited to data analysis.

9. Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories two (2) through eight (8) do not apply but

the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

Suspensions or Terminations
CDC IRBs have authority to suspend or terminate approval of research when it is found that a previously approved research protocol is not being conducted in accordance with the IRB's requirements or that the protocol has been associated with unexpected serious harm to participants. The IRB promptly prepares a statement identifying the reasons for its action. This statement is reported to the investigator and the appropriate institutional officials.

If the research is collaborative and conducted under a funded agreement, notification to the awardee will be made by the Grants Management Officer or the Contracting Officer. Suspensions and terminations will be reported to OPRR by the CDC Deputy ADS.

Exempt Research
Research may be exempt from IRB review. CDC uses the criteria for exemption as described in 45 CFR 46.101. The Deputy ADS makes the final determination whether research is exempt. Documentation of the exemption (CDC form 0.1255) must include the specific category in 45 CFR 46.101 justifying the exemption. Each exempt research study is tracked in the protocol tracking system. Exempt research is reviewed on an annual basis to determine whether it continues to meet the criteria for exemption.

It should be stressed, however, that exemption from IRB review does not relieve the investigator from conducting ethically sound research. For example, it is still important to protect the confidentiality of identifiable data. Also, It may be appropriate to consent participants.

Note: The exemption criteria below do not apply to research involving prisoners, fetuses, pregnant women, or human *in vitro* fertilization.

1. Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as research on regular and special education instructional strategies, or research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

2. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior unless: information obtained is recorded in such a manner that human participants can be identified, directly or through identifiers linked to the participants; and any disclosure of human participants' responses outside the research could reasonably place the participants at risk of criminal or civil liability or be damaging to the participants' financial standing, employability, or reputation. (Examples include: the collection of sensitive data regarding the subjects' [or relatives' or associates'] possible substance abuse, sexuality, criminal history or intent, medical or psychological condition, financial status, or similarly compromising information.)

Note: The above exemption of research involving survey or interview procedures or observation of public behavior, does not apply to research with children except for research involving observations of public behavior when the investigator(s) does not participate in the activities being observed.

3. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt if the human participants are elected or appointed public officials or candidates for public office; or federal statute(s) require(s), without exception, that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.

Note: CDC can use this exemption criterion only in the case where a 308(d) Assurance of Confidentiality has been obtained to cover the research.

4. Research, involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that participants cannot be identified, directly or through identifiers linked to the participants.

Note: "Existing data" means data that was in existence before the study began. If a link is created by an investigators, even temporarily, for research purposes, this criterion is not met. If a temporary link is created by clinical staff who already have access to the data, this criterion is met.

5. Research and demonstration projects which are conducted by or subject to the approval of department or agency heads, and which are designed to study, evaluate, or otherwise examine: public benefit or service programs; procedures for obtaining benefits or services under those programs; possible changes in or alternatives to those programs or procedures; or possible changes in methods or levels of payment for benefits or services under those programs.

6. Taste and food quality evaluation and consumer acceptance studies, if wholesome foods without additives are consumed or if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

Investigators should submit CDC form 0.1255, *Documentation of Exemption Determination for Protocol*, with a brief description of the research or a protocol.

To facilitate the flow of IRB items in the HSO, new protocols, amendments, continuations, terminations, and exemptions should be e-mailed to the "Human Subjects Review-OD" mailbox. This mailbox can be accessed by all HSO staff. If sent by interoffice mail or delivered in person, please send/deliver to Sheila Franklin (building 16, room 4325.01; mailstop D-50)**.**

Confidentiality Protection

Confidentiality protection is an assurance that researchers will greatly limit disclosures and will not be compelled (primarily under subpoena or court order) to disclose sensitive[1] data collected on human research participants. It is generally sought when the information being collected is of such a sensitive nature (data collection on such areas as sexual practices, use of alcohol or drugs, illegal conduct, information the disclosure of which could lead to social stigmatization, etc.) that the respondents would not likely furnish the information or might not provide valid responses (thereby possibly compromising research objectives) unless such an assurance is given.

CDC and ATSDR must comply with Federal access statutes that govern disclosures. Unless an exemption applies, Federal agencies must supply responses to Freedom of Information Act (FOIA) requests. When appropriate, the FOIA (b)(6) exemption-- covering information the release of which would constitute a "clearly unwarranted invasion of personal privacy"--can be used to enable sensitive individually identified data being requested under that Act to be withheld. However, under an appeal, a court might rule in favor of disclosure. While strong objections would be raised, there is a possibility the agency could be compelled to furnish the data in identifiable form. Further, the Privacy Act, while providing adequate protection for the majority of research projects involving individually identified data, nevertheless permits disclosures under 12 conditions, including routine uses listed in the system notice and court orders. Additionally, the Act does not provide protection for dead individuals nor institutions.

There are two types of confidentiality protections available to CDC researchers. The first, called a "Confidentiality Assurance," provides protection to both individuals and institutions. This assurance, authorized under Section 308(d) of the PHS Act, is used for studies conducted by CDC staff and/or contractors. The second, known as a "Certificate of Confidentiality," authorized under Section 301(d) of the PHS Act, provides protection only to individuals, and is primarily used for grants or cooperative agreement projects funded by CDC and ATSDR.

Confidentiality can be promised ONLY when a formal application for 308(d) or 301(d) confidentiality protection for the project has been made and approval has been granted by the CDC Confidentiality Review Group (CRG). The CRG is comprised of: a representative from the Office of General Counsel, a medical ethics expert from the office of the CDC Associate Director for Science, the CDC Privacy Act Officer, the NCHS Confidentiality Officer, and senior level management epidemiologists and statisticians. The application procedure and criteria for approval differ for the two types of confidentiality protection.

308(d) Assurances of Confidentiality

The criteria for approval for a confidentiality assurance include a determination by the CRG that the applicant has provided responses that clearly indicate that:

1. the individual or establishment will not furnish or permit access to data being requested unless a confidentiality assurance is given;

2. the assurance is important to the protection of the individual or institution;

3. the information cannot reliably be obtained from other sources not requiring an assurance;

4. the information is essential to the project's success;

5. giving the confidentiality assurance will not restrain CDC from carrying out its responsibilities; and

6. the advantages of assuring confidentiality outweigh the disadvantages.

Each CRG member also considers the adequacy of the Assurance of Confidentiality Statement and the Confidentiality Security Statement (discussed below in application procedures) and either concurs or raises issues that must be answered that would enable the member to approve the application. If the program does not satisfactorily answer all concerns, approval for confidentiality protection will not be granted; the decision of the CRG must be unanimous.

To apply for a Confidentiality Assurance:

1. Researcher discusses project particulars with CIO Associate Director for Science or CDC Confidentiality Officer for a preliminary determination of whether the protection seems warranted;

2. A draft application is submitted to the CDC Confidentiality Officer, Management Analysis and Services Office (MASO), containing a completed CDC form 0.970, and attaching:
   (a) Justification Statement summarizing the project's programmatic purpose, the type of data to be collected, and the uses to be made of the information;

   (b) A response to the six issues that constitute the criteria for approval of the request;

   (c) A formal Assurance of Confidentiality Statement delineating the uses to be made of the data;

   (d) A Confidentiality Security Statement detailing the stringent safeguarding measures that will be in place to ensure that the promise of confidentiality is not jeopardized by staff handling the data;

   (e) A statement as to whether CDC IRB approval is being sought (or whether the project is exempt) along with a copy of the protocol.

3. When comments and suggestions for change have been finalized, the package is submitted to the CIO Director for signature on CDC form 0.970 and transmitted to MASO, who coordinates review by the CRG. When CRG approval is obtained, the Director, MASO signs the 308(d) confidentiality assurance approval.

301(d) Certificates of Confidentiality

Interim PHS guidance indicates that under the statute the confidentiality certificate can be granted only:

1. If the project can be considered research (i.e., a systematic investigation designed to develop or contribute to generalization knowledge;

2. When the research is of a sensitive nature where the protection is judged necessary to achieve the research objectives. Research can be considered sensitive if it involves the collection of information in categories such as: information relating to sexual practices, use of alcohol or drugs, illegal conduct, information that could reasonably be damaging to one's financial employability or reputation; information in a patient's medical record, the disclosure of which could reasonably lead to social stigmatization or discrimination, etc.

Additional elements considered by the CRG include reviewing the protocol, relying upon the approval of the local IRB but also looking carefully at the protocol from a perspective of what the research question is, whether the design addresses the research question, what types of data are collected, how the data are handled and protected, and evaluating whether the need for additional protections of confidentiality provided by a certificate are warranted. The consent form is carefully reviewed and language added describing the certificate's protection.

To apply for a 301(d) confidentiality certificate:

1. Researcher (generally the Principal Investigator (PI) at the local site or the CDC Project Officer) discusses project particulars with the CDC Confidentiality Officer for a preliminary determination of whether the protection seems warranted;

2. A draft application letter is submitted to the CDC Confidentiality Officer, Management Analysis and Services Office, addressing:
   (a) project title, source of funding, grant or cooperative agreement number;

   (b) whether identifying information will be collected;

   (c) purpose of project, what the study is attempting to learn, study methods, how long data will be collected, how subjects will be identified;

   (d) sensitive information to be collected, safeguarding measures that will be in place to protect the data, effect upon respondents if the data does not have confidentiality protection, and instances in which the institution might be called upon to use the certificate to withhold data;

   (e) If project is testing for reportable communicable diseases, how the project intends to comply with policies set out in 8/9/91 memo on that subject from the Assistant Secretary for Health;

   (f) States that the project complies with protection of human subjects regulation (45 CFR 46),

specifically that it has been reviewed by an Institutional Review Board (IRB), and includes a copy of the IRB approval. Addresses if CDC IRB review is needed.

Each package should also include: a more detailed description of the project (the protocol), data collection forms, consent forms, introductory letters, and copy of IRB approval(s).

4. When comments and suggestions for change have been finalized, the package is submitted to MASO, who coordinates review by the CRG. When CRG approval is obtained, the Director, CDC signs the 301(d) confidentiality certificate.

NOTE: Application may be made directly by outside institutions, but if there are a number of sites conducting the same project, a consolidated application should be done, with the CDC/ATSDR project officer addressing all required elements in an application memo, and each site providing a short letter stating that they wish to apply for the confidentiality certificate, (attaching local IRB approval and consent forms).

The application process for confidentiality assurances or certificates can take 2-3 months due to the number of applications and the need for the applicant to provide a satisfactory response to all issues raised by MASO and CRG members.

It should be noted that there are some disadvantages to obtaining confidentiality protection. The primary disadvantage is the inability to freely share individually identified data with other researchers. There is also the need to anticipate all individually identified data sharing at the outset. Except for the purposes stated at the time of data collection, no other disclosures should be made without the consent of the respondents. While disclosures are permitted if written consent from respondents is obtained, this is generally not feasible. Finally, it should be remembered that stringent physical, administrative and procedural safeguards should be in place to protect confidential data.

For further information or instructions, contact Betsey Dunaway, the CDC Confidentiality Officer, MASO, at (404) 639-2942.

Cooperative Research

Cooperative research projects are those projects which involve more than one institution and are normally supported through grants, contracts, cooperative agreements or similar arrangements. Where the principal grantee or primary contractor involve additional institutions in the research, they remain responsible to CDC for safeguarding the rights and welfare of human participants. However, each cooperating institution shall comply with the Federal Regulations except that in complying with the Federal Regulations institutions may use joint review, reliance upon the review of another qualified IRB, or similar arrangements aimed at avoidance of duplication of effort, with approval of OPRR. The HSO (for nonfunded research) and PGO (for funded research) will be responsible for ensuring that collaborative institutions have OPRR-approved assurances of compliance with the Federal Regulations and that collaborative institutions' IRBs have reviewed and approved the research.

CDC and Collaborating Institution IRB Reviews of Cooperative Research

For cooperative research conducted between CDC and another institution, a protocol and consent form should be developed that will be reviewed by the CDC IRB and the collaborating institution IRB. It is recommended that the CDC IRB review the protocol and consent form prior to the review by the collaborating institution IRB. If the collaborating institution IRB changes the protocol and any supplementary documents, those changes must also be reported to and approved by the CDC IRB (and vice versa).

Reliance on Another IRB

When CDC is one of the collaborating institutions in a collaborative research project, CDC's IRB will review and approve the research protocol. On rare occasions, CDC may choose to rely upon the review of another IRB, (i.e., defer to another IRB).

Criteria for Reliance on Another IRB

CDC IRB review of a research project conducted in part by CDC investigators may be deferred to an OPRR-approved, non-CDC IRB when ***all*** of the following conditions are met:

1. The Principal Investigator is not an employee, contractor, visiting scientist or fellow of CDC. This policy does not apply to a CDC employee who is assigned to another agency and who functions as an employee of that agency and lists his/her affiliation with the other agency and not with CDC.

2. CDC does not fund the research study. That is, for example, no grants, cooperative agreements or contracts are issued by CDC in support of the research. In-kind salary support of the CDC investigator is allowed under this criterion.

3. CDC investigators do not have any direct interaction with study participants or possess individually identifiable data from the study.

4. The study has been granted approval by a non-CDC IRB of an organization that has a MPA

from OPRR and is responsible for participant recruitment.

5. The study involves no more than minimal risk and does not address a controversial topic. Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. Controversial topic means a sensitive topic such as illegal behaviors, sexual behavior practices, or psychiatric illness; involves a vulnerable population as defined in the Federal Regulations; or is of particular interest to the DHHS or Congress.

CIO Responsibilities

The CIO submits a CDC form 0.1250, *Request for New Protocol Approval*, for reliance on another IRB to the Deputy ADS. (Although the intent is to rely on the IRB of another MPA institution, the HSO still needs to track the disposition of the protocol.) The request should address each of the criteria listed above in the following manner:

1. the identity of the Principal Investigator and his/her affiliation and the names of the CDC collaborators and their roles in the research study.

2. a statement that CDC has not contributed funds to the study.

3. a statement that CDC will not have direct interaction with study participants nor possess personal identifiable data.

4. evidence that an OPRR-approved, non-CDC IRB has approved the study; provide the name, address, phone number of the IRB's Chair and of the IRB's administrator.

5. a statement that the study involves no more than minimal risk and involves no controversial issues.

A copy of the approved study protocol and consent forms must be attached to the written request. If the research study is approved for review by another IRB, the HSC will submit a copy of any amendments or changes submitted to the non-CDC IRB as well as copies of all annual reports on the protocol and certifications of annual IRB review and approval.

HSO Responsibilities

The CDC Deputy ADS will determine whether reliance on another IRB is appropriate. If a decision is made to defer, the Deputy ADS will contact the non-CDC IRB to complete a Cooperative Amendment and submit it to OPRR.

When the Cooperative Amendment is approved by OPRR, the Deputy ADS will notify the HSC who, in turn, will notify the CDC investigator.

CDC's decision to defer protocol review will be reviewed on an annual basis by the Deputy ADS; an annual report and certification of IRB approval by the non-CDC IRB will be reviewed by the

Deputy ADS. The study protocol will be assigned a CDC protocol number and tracked as an active study protocol.

Non-Federally-Funded Research

Assurance of Compliance from Collaborating Institutions and IRB Review

CDC will enter into collaborative research studies only when the collaborating institution(s) has provided evidence of an Assurance of Compliance with the Federal Regulations and certification of IRB review and approval. Evidence of assurance and IRB certification of review for nonfunded collaborative research will be the responsibility of the HSO.

When a research protocol is submitted to the CDC IRB for review, the CDC investigator will notify the HSO (Atlanta), the IRB Administrator (NCHS), or the IRB Chair (NIOSH) of all collaborating institutions on the research study. The HSO will determine whether each collaborating institution has an OPRR-approved assurance.

Domestic Assurances

For a domestic institution that does not have an assurance, the HSO will notify the CDC investigator that the collaborating institution(s) will need to obtain a single project assurance (SPA). The HSO will prepare the respective SPA Packet(s). For an independent investigator not affiliated with an institution, completion of an Agreement for an Independent Investigator (AII) is required.

*Procedure for CDC Investigators Completing a **Domestic SPA** Document*:

1. The CDC investigator will be given an electronic copy of the SPA Packet specific for the institution/protocol or the SPA Packet can be mailed directly to the collaborating institution if the CDC investigator prefers the HSO to send the SPA packet to institution in which the research project is being conducted.

2. The first page of the SPA must be typed on appropriate collaborating institutional letterhead.

3. It is the responsibility of the investigator to secure the following signatures:
   (a) If the institution has its own IRB, three signatures are needed:

   (1) signature I, authorized official of the institution providing the assurance;

   (2) signature III, IRB chairperson. The IRB chairperson must also sign the IRB roster, which makes up the last page of the SPA;

   (3) signature IV, responsible project investigator. This is the coinvestigator at the collaborating institution, the same individual named in Part 2 (I) and Part 3.

   (b) If the institution does not have its own IRB, it must rely on the IRB of another institution,

preferably one in the geographic area in which the study is to be conducted. The designated IRB MUST be affiliated with an institution that holds an OPRR-approved MPA. The investigator will need to obtain four signatures:

(1) signature I, authorized official of the institution providing the assurance;

(2) signature II, authorized official of the institution with the IRB;

(3) signature III, IRB chairperson. The IRB chairperson must also sign the IRB roster, which makes up the last page of the SPA;

(4) signature IV, responsible project investigator. This is the coinvestigator at the collaborating institution, the same individual named in Part 2 (I) and Part 3.

(c) OPRR requires, if possible, for the institution to rely on an IRB in their geographic area in which the study is to be conducted. If there is no local IRB, the institution may request that the CDC IRB serve as the IRB of record; however, the CDC IRB must have access to knowledge about the local setting.. The investigator will need to obtain two signatures:

(1) signature I, authorized official of the institution providing the assurance;

(2) signature IV, responsible project investigator. This is your coinvestigator at the collaborating institution, the same individual whom you named in Part 2 (I) and Part 3.

In scenario "3c" above, CDC's Human Subjects Office will obtain all remaining signatures (IRB chair.:

Signature Notes: The authorized official signing in signature block I must be someone at the institution who can "bind" the institution to the agreement (i.e., the SPA). Further, THE AUTHORIZED OFFICIAL (SIGNATURE "I") AND THE IRB CHAIRPERSON MAY NOT BE THE SAME INDIVIDUAL DUE TO THE APPEARANCE OF A CONFLICT OF INTEREST. The constitution of the IRB is defined in 45 CFR 46, Section 107 a-f. Specifically, the IRB is to have at least five members, with varying backgrounds; will not consists entirely of men or entirely of women nor consist entirely of members of one profession; shall include at least one scientist and one nonscientist; and shall include at least one member who is not otherwise affiliated with the institution.

A roster of IRB members from the IRB that reviewed the protocol must be attached to the assurance. This roster is to include the IRB Chairperson's signature.

The SPA must not be signed by ANYONE until the protocol is approved by the collaborating IRB. The paragraph immediately above the signature blocks reads: "The officials signing below assure that the project referenced above was approved by the IRB of the date indicated and the project will be conducted in accordance with the requirement of Part 46, Title 45 of the

Code of Federal Regulations and this Assurance document. A dated roster listing the current membership of the designated IRB is attached."

4. The collaborating institution's IRB-approved consent form must be sent along with the SPA document.

5. For scenarios "3a and 3b" above, Forward the signed/completed SPA, consent form(s), and CDC cover letter to OPRR:

Mr. George Gasparis
Assurance Branch, Division of Human Subject Protections
Office for Protection from Research Risks (OPRR)
6100 Executive Boulevard, Suite 3B01
National Institutes of Health
Rockville, Maryland 20852)

For scenarios "3c" above return the signed SPA and consent form(s) to CDC HSO:

Mrs. Virginia Talley
Assurance Coordinator
CDC Mailstop D50
1600 Clifton Road, NE
Atlanta, GA 30333
(404) 639-7621
(404) 639-7341 (FAX)

6. Once the documents are received, the HSO will review the documents for completeness and forward them to OPRR for approval.

7. OPRR will then review the SPA and consent form(s) and, if all is in order, issue a SPA number. (In an emergency, a signed facsimile may be sent while the original is in transit.)

8. Once approved and given a number, OPRR will send one signed original to CDC's HSO and one to the collaborating institution.

*Procedure for CDC Investigators Completing a **Domestic AII** Document*

The Agreement for an Independent Investigator is for use by investigators who are participating in an HHS-conducted or supported research project when acting independent (i.e. not affiliated with) of any hospital, clinic, or other facility. An agreement is not required for referral physicians or other physicians to whom research subjects are returned by an investigator who maintains responsibility for management of subjects.

1. The CDC investigator will be given an electronic copy of the AII specific for the collaborator with whom the research project is being conducted.

2. The first page of the AII must be typed on appropriate independent investigator letterhead.

3. It is the responsibility of the CDC investigator to secure the signature of the collaborating independent investigator (D1.(b)) when CDC has been designated the IRB of record.

4. Return the signed document to CDC HSO:

   Mrs. Virginia Talley
   Assurance Coordinator
   CDC Mailstop D50
   1600 Clifton Rd., NE
   Atlanta, GA 30333
   (404) 639-7621
   (404) 639-7341 (FAX)

5. After CDC's IRB approves the protocol, the HSO will send the AII to OPRR for approval. OPRR will review the AII and, if in order, assign an AII number.

   (In an emergency, a signed facsimile may be sent while the original is in transit.)

6. Once approved and given a number, OPRR will send one signed original to CDC's HSO and one to the collaborating independent investigator.

Foreign Assurances

For a foreign institution that does not have an assurance, the HSO will prepare an international SPA or an international cooperative project assurance (CPA).

An international SPA is similar to the domestic SPA in that the assurance is protocol-specific, i.e., it references the protocol's title and number. The SPA may be used for closely related protocols, however, e.g., a substudy of the protocol named on the SPA. Signatories to the SPA attest to review and approval of the protocol(s) by the designated ethics committee (EC).

An international CPA, conversely, covers for five years all research protocols involving human participants conducted with the foreign institution. The CPA, however, is not CDC-specific; rather, it was created with the intention of making it a U.S. government-wide document provided that the other U.S. government entities participate in OPRR's International Cooperative Protocol Research Program (ICPRP) under the review authority of OPRR. CDC participates in this program, which is to be used when an existing collaboration has proven to be productive for CDC and the host country institution(s) (i.e., as evidenced by successful SPAs with the organization), and joint research projects are anticipated for the near and distance future. The ICPRP consists of multiple protocol collaborations involving or potentially involving multiple sites in one or more host countries. The ICPRP collaboration must be approved by the Deputy ADS. The CDC international CPA will be reserved for multi-site, multi-protocol international collaborations involving the research areas listed below, and will be invoked only after CDC has an established history of productive collaboration with the host country institution. Single protocol collaborations will be covered through the international SPA mechanism (see above). Each research protocol must be reviewed by a CDC IRB and an OPRR-approved designated EC (EC)

within each host country institution, e.g., the ministry of health. Alternative arrangements are available when the host country institution does not have its own EC.

ICPRP collaborations include:

1. Epidemiology protocols in infectious diseases, including HIV, sexually transmitted diseases, and tuberculosis.

2. Epidemiology protocols in environmental and occupational health.

3. Vaccine-related protocols.

4. Therapeutic intervention protocols in infectious diseases, including HIV, sexually transmitted diseases, and tuberculosis.

5. Therapeutic intervention protocols in environmental health.

6. Community intervention protocols in infectious diseases, including HIV, sexually transmitted diseases, and tuberculosis.

7. Community intervention protocols in environmental and occupational health.

International Single and Cooperative Project Assurances (CPAs)

The CDC investigator should explain to his/her colleagues at the host country institution(s) with whom he/she will be conducting the research, the need for CDC and host country review of the protocol. Also, the need for and requirements of an assurance are discussed and agreed upon. The CDC investigator subsequently provides a packet of assurance material to each collaborating host country institution. The host country institution then convenes the appropriate EC or, in the case of a SPA, may decide to rely on another EC.

Procedure for CDC Investigators in Obtaining an ***International CPA***:

Since the CPA is not protocol-specific, the CPA document can be completed months in advance of a protocol coming to the HSO for review and approval by CDC's IRB. The following instructions apply when an investigator anticipates working collaboratively with a foreign institution:

1. The CDC investigator will be given an electronic copy of the CPA specific for the institution in which the research project is being conducted.

2. The CPA must be in English; OPRR only accepts and approves English versions. However, OPRR will sign a foreign translation when accompanied by the English version (both documents must have original signatures). Thus, the CDC investigator may need to have the assurance translated into the official language of the host country if the host country so wishes. FYI, the HSO provides French and Spanish translations.

3. The first page of the CPA must be typed on appropriate host country institutional letterhead. If letterhead is not available, an official stamp or seal may be used at each signature.

4. It is the responsibility of the CDC investigator to secure the following signatures:
   (a) If the institution has its own EC, the investigator will need to obtain two signatures:

   (1) signature A, authorized official of the institution providing the assurance;

   (2) signature D, Ethics Committee Chairperson. The EC chairperson must also sign the IRB roster, which makes up the last page of the CPA.

   (b) If the institution does not have its own IRB, it must rely on the IRB of another institution in the same country/geographic area in which the study is to be conducted. The CDC investigator will need to obtain four signatures:

   (1) signature A, authorized official of the institution providing the assurance;

   (2) signature C, authorized official of the institution with the EC;

   (3)s ignature D, IRB chairperson. The IRB chairperson must also sign the IRB roster, which makes up the last page of the SPA.

   In the above scenarios, CDC's Human Subjects Office will obtain all remaining signatures.

Signature Notes: The authorized official signing in signature block A must be someone at the institution who can "bind" the institution to the agreement (i.e., the CA).

A dated roster of EC members must be attached to the assurance. This roster is to include the EC chairperson's signature.

5. These documents should be hand carried or sent by express mail to CDC HSO:

   Mrs. Virginia Talley
   Assurance Coordinator
   CDC Mailstop D50
   1600 Clifton Rd., NE
   Atlanta, GA 30333
   (404) 639-7621
   (404) 639-7341 (FAX)

   (In an emergency, a signed facsimile may be sent while the original is in transit.)

6. The HSO will send the CPA to OPRR who will then review it. If in order, OPRR will issue a CPA number.

   (In an emergency, a signed facsimile may be sent while the original is in transit.)

7. Once approved and given a number, OPRR will send the signed originals to CDC's HSO. The

HSO will forward one original English and one host country language original (if applicable) to the CDC investigator's CIO/HSC, who will then forward to the CDC Investigator. The CDC investigator will forward to the appropriate host institution official.

*Procedure for Obtaining an **International SPA***:

1. The CDC investigator will be given an electronic copy of the SPA specific for the institution/protocol in which the research project is being conducted.

2. The SPA must be in English; OPRR only accepts and approves English versions. However, OPRR will sign a foreign translation when accompanied by the English version (both documents must have original signatures). Thus, the CDC investigator may need to have the assurance translated into the official language of the host country if the host country so wishes. FYI, the HSO provides French and Spanish translations.

3. The first page of the SPA must be typed on appropriate host country institutional letterhead. If letterhead is not available, an official stamp or seal may be used at each signature.

4. It is the responsibility of the CDC investigator to secure the following signatures:
   (a) If the institution has its own IRB, the investigator will need to obtain three signatures:

   (1) signature I, authorized official of the institution providing the assurance

   (2) signature III, IRB chairperson. The IRB chairperson must also sign the IRB roster, which makes up the last page of the SPA.

   (3) signature IV, responsible project investigator. This is the host country coinvestigator at the collaborating institution, the same individual named in Part 2 (I) and Part 3.

   (b) If the institution does not have its own IRB, it must rely on the IRB of another institution, preferably one in the same country/geographic area in which the study is to be conducted. The CDC investigator will need to obtain four signatures:

   (1) signature I, authorized official of the institution providing the assurance

   (2) signature II, authorized official of the institution with the IRB

   (3) signature III, IRB chairperson. The IRB chairperson must also sign the IRB roster, which makes up the last page of the SPA.

   (4) signature IV, responsible project investigator. This is the host country coinvestigator at the collaborating institution, the same individual named in Part 2 (I) and Part 3.

   (c) Under rare circumstances, it may not be possible to rely on an IRB in the host country/geographic area in which the study is to be conducted (one may not be in

existence). In this case, the institution may elect to request that the CDC IRB serve as the IRB of record; however, a local representative from the community in which the study is to be conducted is required to sit on the IRB for review of the protocol. The CDC investigator will need to obtain two signatures:

(1) signature I, authorized official of the institution providing the assurance

(2) signature IV, responsible project investigator. This is the host country coinvestigator at the collaborating institution, the same individual named in Part 2 (I) and Part 3.

In the above three scenarios, CDC's Human Subjects Office will obtain all remaining signatures.

Signature Notes: The authorized official signing in signature block A must be someone at the institution who can "bind" the institution to the agreement (i.e., the SPA).

A dated roster of current IRB members from the IRB that reviewed the protocol must be attached to the assurance. This roster is to include the IRB Chairperson's signature.

The SPA must not be signed by ANYONE until the protocol is approved by the designated collaborating IRB.

5. The documents should be hand carried or sent by express mail to CDC HSO:

Mrs. Virginia Talley
Assurance Coordinator
CDC Mailstop D50
1600 Clifton Rd., NE
Atlanta, GA 30333
(404) 639-7621
(404) 639-7341 (FAX)

(In an emergency, a signed facsimile may be sent while the original is in transit.)

6. After CDC's IRB approves the protocol, the HSO will ask the CDC investigator to send a final "clean" copy of the IRB-approved protocol/consent forms, etc., incorporating all changes. A copy will be sent to OPRR with the signed SPA. OPRR will then review both the SPA and the protocol/consent forms, etc., and, if all is in order, issue a SPA number.

   (In an emergency, a signed facsimile may be sent while the original is in transit.)

7. Once approved and given a number, OPRR will send the signed originals to CDC's HSO. The HSO will forward one original English and one host country language original (if applicable) to

the CDC investigator, who will the forward to the appropriate host institution official.

Note: Once a protocol is submitted to and reviewed and approved by the CDC IRB, the approved protocol should be submitted to the designated host country institution EC for review and approval. A copy of the host institution's EC report must then be sent to CDC's HSO to become a permanent part of the record.

Federally-Funded Research

General Information for Grants, Cooperative Agreements and Contracts
Assurance of Compliance with 45 CFR 46 and Certification of IRB Review
Federal funds administered by CDC may not be expended for research involving human participants unless the requirements of 45 CFR 46 including all Subparts have been satisfied.

Applications or Proposals Lacking Definite Plans for the Involvement of Human Participants
Certain types of applications for grants, cooperative agreements or contracts are submitted to CDC with the knowledge that human participants may be involved within the funding period but definite plans for their participation would not normally be set forth in the application or proposal. These include activities such as institutional type grants where selection of specific projects is the institution's responsibility; research training grants where the activities involving participants remain to be selected; and projects in which human participants' involvement will depend upon completion of instruments or working with the community. These applications need not be reviewed by an IRB before an award can be made. However, except for research exempted or waived under the Federal Regulations, no human participants may be involved in any project supported by the award until the project has been reviewed and approved by an IRB (45 CFR 46.118).

During the initial administrative review of the applications or proposals by PGO, the application checklist must be reviewed for the use of human participants. A certification of Assurance of Compliance and IRB review (*Optional Form 310* or designation on the *Application Form 398*) must be provided with the application or proposal if human beings are involved. If certification is not provided, PGO must request it from the applicant or offeror.

Grants and Cooperative Agreements[6]
Program Announcement
1. At the time of developing the Program Announcement:
   If the proposed activities are research, the CIO will include in the Other Requirements section of the Program Announcement the phrase "Human Subject Requirements." This statement alerts PGO to include the following human participants language:

   "If the proposed project involves research on human participants, the applicant must comply with the Department of Health and Human Services Regulations (45 CFR 46) regarding the protection of human research participants. Assurance must be provided to demonstrate that the project will be subject to initial and continuing reviews by an appropriate institutional review board. The applicant will be responsible for providing evidence of this Assurance in accordance with the appropriate guidelines and forms provided in the application kit.

[5]The Grants Management Operations Manual can be found on the HSO intranet homepage at http://intranet.cdc.gov/od/ads/hsr2.htm

In addition to other applicable committees, Indian Health Service (IHS) institutional review committees also must review the project if any component of IHS will be involved with or will support the research. If any American Indian community is involved, its tribal government must also approve that portion of the project applicable to it.

Unless the awardee holds a MPA, a SPA is required, as well as an Assurance for each subcontractor or cooperating institution that has immediate responsibility for human participants.

The Office for Protection from Research Risks (OPRR) at the Department of Health and Human Service negotiates Assurances for all activities involving human participants that are supported by the Department."

If the research project will have CDC scientists as co-investigators, the CIO will insert the following under the CDC Activities listed under the Program Requirements in the Program Announcement:

" Assist in the development of a research protocol for IRB review by all institutions participating in the research project.

The CDC IRB will review and approve the protocol initially and on at least an annual basis until the research project is completed."

In the Evaluation Criteria section, the following language should be included:

" If human subjects protections is or may be required, the following criterion must also be included:

Does the application adequately address the requirement of 45 CFR 46 for the protection of human subjects (as determined by an Objective Review Group)? (Not scored)

_____ Yes _____ No Comments: _____"

Review of Applications by an Objective Review Group (ORG)

Prior to review of the application by the ORG, the CIO Program Official responsible for the review must determine that all human participants' information has been included in the application so that the ORG can adequately evaluate protection for the participants. The CIO HSC also must advise the ORG of their responsibility to evaluate the protection of the participants.

The ORG is expected to review the use of human participants as described in the protocol in the application. The review is to take into consideration the risks to the participants, the adequacy of protection against these risks, the potential benefits of the proposed research to the participants, and the importance of the knowledge to be gained.

<u>The ORG may recommend:</u>

1. approval of the application without any human participants restrictions;

2. approval of the application but with comments made to the applicant regarding human participants protections;

3. limitations of the work proposed, the imposition of restrictions, the elimination of concerns relating to the protection of human participants prior to the release of an award; or

4. disapproval of the application if the research risks are sufficiently serious and protection against the risks is so inadequate as to make the entire application unacceptable.

A section must be provided in the Summary Statement reflecting the evaluation of the use of the human participants. If there are any restrictions, limitations, concerns and comments relating to the human participants, they must be addressed in the Summary Statement.

Review and Award by PGO

Pre-award Review of Applications:

All applications having unresolved human participants concerns must have documentation from the CIO of their satisfactory resolution. If this is not possible prior to the award, information regarding any restrictions must be transmitted in writing to the Grants Management Branch for inclusion in the award notice.

For each application recommended for approval, which is likely to be funded and which requires negotiation of an Assurance of Compliance (when the institution is not a MPA institution), PGO will forward to the OPRR Assurance Coordinator (AC) a request for negotiation of an Assurance of Compliance using OPRR's designated format. Note: if CDC investigators are involved in the research, PGO must identify CDC as one of the performance sites on the request.

The following should be attached to the request:

1. the application,

2. summary statement,

3. addenda, and

4. information identifying the individual(s) at CDC who should be notified when the negotiation is completed and the Assurance of Compliance approved.

For applications involving human participants from (1) foreign/international organizations and their foreign subcontractors who are conducting research involving human participants and (2) domestic institutions (with or without MPAs) who are subcontracting with a foreign/international organization that is participating in the research, the Grants Management Branch must submit the following information to the Deputy ADS:

1. PGO contact's name, title, telephone number, and mailstop;

2. applicant organization's name, address, telephone number for the individual who signed the application, and the application number;

3. names and locations of all participating organizations.;

4. clear indication for applicant and each participating organization as to whether it has a MPA;

5. project title and projected budget period start date;

6. grant or cooperative agreement number; and

7. name, telephone number, and mailstop for the CDC Official.

The Deputy ADS will inform the Grants Management Branch if any participating organizations already have Assurances of Compliance on record and provide the Assurance of Compliance numbers. If there is no Assurance of Compliance on record, the Deputy ADS will request it, and send a copy of the request to PGO. It will be the responsibility of the Grants Management Branch to code awards appropriately and track the receipt of the Assurances of Compliance.

During the month of September, when there is insufficient time to obtain the SPA before the award must be made to meet CDC's award deadlines, OPRR has agreed to allow awards with restrictions (language for the restriction provided by OPRR) on the use of funds for research involving humans.

Where the research will be conducted by cooperating institutions, all of the cooperating institutions must have Assurances of Compliance on file with OPRR.

Before a year has elapsed between the IRB approval date certified on the *Optional Form 310* and the anticipated award date, PGO requires IRB re-review and certification on a validly dated *Optional Form 310* prior to award.

The Grants Management Branch places a code(s) in the Grants Management Information System (GMIS) award module for each award that involves human participants. This code(s) serves as a reminder that the project involves human participants and that annual IRB reviews is required.

Review and Award of Noncompeting Continuation Applications
PGO will determine the presence and completeness of the *Optional Form 310* or designation on the *Application Form 2590*. Certification must be within the 12 months immediately preceding the requested award date. No award will be made until certification is received by PGO.

Tracking CDC IRB Reviews
In some cases CDC scientists will function as investigators for some cooperative agreements. Under the Federal Regulations, each cooperating institution in a research project is responsible for

reviewing the research. For those cooperative agreements in which there are CDC coinvestigators, CDC is defined as one of the cooperating institutions and must review the research project just as the awardee and other participating organizations (e.g., subcontractors) must do. PGO needs to track initial and annual CDC, awardee, and other organization IRB reviews. CDC coinvestigators should send copies of their CDC IRB approval memos to the Grants Specialist.

The following procedures will be implemented:
When a CIO submits funding memoranda for new grants or cooperative agreements and for non-competing continuation cooperative agreements, it will attach to the funding memo the *Human Subjects Research Tracking Form* which describes whether the award will be research involving human participants, whether CDC coinvestigators are involved and if the CDC IRB has reviewed and approved the protocol. If an exemption is claimed on the *Human Subjects Research Tracking Form* by the CIO, PGO will promptly forward the form to the Deputy ADS for concurrence. Under the Federal Regulations, OPRR retains final judgment as to whether a particular activity is exempt. However, OPRR has delegated that authority to CDC.

Umbrella Single Project Assurances of Compliance **(Modified SPA)**
CDC makes awards to umbrella organizations that do not conduct research; rather, these organizations provide administrative support to research institutions. Examples include the Association of Schools of Public Health (ASPH) and the Association of Teachers of Preventive Medicine (ATPM). These organizations have members who conduct research involving human beings. Individual subprojects are awarded to members through the primary award under a primary project period as specified in an official Program Announcement so long as a subproject starts during the primary project period and terminates with the end of the project period.

OPRR and CDC have worked out an arrangement whereby these umbrella organizations will be covered under a SPA, which has been modified to reflect the organizational relationship between the umbrella organization and its members. Further, these umbrella organizations will not be required to convene IRBs for review of research funded through subprojects to members. Member organizations will have either a MPA or will obtain a SPA. Member organizations will convene IRBs and review and approve the research.

The following process will be used for obtaining the modified SPA for umbrella organizations:
1. When CDC plans to fund an umbrella organization, PGO will notify the appropriate AC at OPRR and refer to the "modified" SPA. At the same time, PGO may send the modified SPA to the awardee. The awardee will complete the SPA on its letterhead and send it to OPRR.
2. OPRR will approve the SPA and notify PGO.

3. If a sub-awardee, OPRR will approve the SPA for the sub-awardee and notify PGO.

4. PGO will certify that the sub-awardee has completed *CDC Optional Form 0.310*, indicating IRB approval.

Contracts and Purchase Orders

Request for Contract (RFC) or Purchase Orders

6. At the time of developing the RFC:
   The CIO HSC sends a *Human Subjects Clearance Research Tracking Form* to PGO stating whether the study is research involving humans participants, whether CDC investigators are participating in the research, and if an exemption is claimed.

   (a) When research involving human participants is developed in the first phase but not conducted until the second phase of a contract:
   At the time the RFC is submitted to PGO, the CIO HSC informs PGO that the study is research involving humans as participants, indicates whether CDC investigators are involved, whether an exemption is claimed, and that the research will not begin until the second phase. Funds are not restricted for phase one. Phase two cannot begin (i.e., funds are restricted or approval to proceed to phase two is withheld) until all Assurances of Compliance and IRB approvals are obtained. If CDC investigators are participating in the research, the CIO HSC must inform PGO of CDC IRB approval before approval is given to the contractor to proceed with phase two.

   (b) When the research protocol involving human participants is described in the contract:
   At the time the RFC is submitted to PGO, the CIO HSC informs PGO that the study is research involving human participants, indicates whether CDC investigators are involved, and whether an exemption is claimed. If CDC investigators are participating, the CDC IRB must approve the research before the award is made. The CIO HSC informs PGO that research is approved by CDC IRB. The Contracts Branch, PGO will promptly forward the *Human Subjects Research Tracking Form* identifying an exemption to the Deputy ADS for concurrence.

2. At the time of issuing the Request for Proposal (RFP):
   In addition to the standard language pertaining to research involving human participants, the RFP will contain the following language when CDC scientists are to be involved as co-investigators in the contract:

   "CDC's Institutional Review Board (IRB) - It is anticipated that this requirement will involve participation by CDC investigators in the research activities. Therefore, the CDC IRB must approve the research protocol prior to contract award. If the CDC IRB approval is not received prior to contract award then a restricted award must be made. Contract awards issued on a restricted basis will prohibit the use of any funds that are associated with the use of human subjects."

3. At the time of developing the Statement of Work for the Request for Task Order or for a services Purchase Order:
   The CIO HSC completes a *Human Subjects Research Tracking Form* with the Statement of Work. The form must identify whether human participants are involved, if CDC staff are participating as co-investigators, and if any exemptions are claimed. The Contracts Branch, PGO, will promptly forward all *Human Subjects Research Tracking Forms* identifying an

exemption to the Deputy ADS for concurrence.

Review of Proposal by a Technical Evaluation Panel

When the *Optional Form 310* is reviewed with the offerors' proposals, the panel reviews it, and the Contract Officer conducts discussions with the offeror about any outstanding Assurance of Compliance issues.

Review and Award by PGO

1. Pre-award Review of Proposals:

   All proposals having unresolved human participants concerns must have documentation from the CIO of their satisfactory resolution. If this is not possible prior to the award, information regarding any restrictions must be transmitted in writing to the Contract Branch for inclusion in the contract.

   For each proposal recommended for approval, which is likely to be funded and which requires negotiation of an Assurance of Compliance (when the institution is not a MPA institution), PGO will forward to the OPRR Assurance Coordinator (AC) a request for negotiation of an Assurance of Compliance using OPRR's designated format. Note: if CDC investigators are involved in the research, PGO must identify CDC as one of the performance sites on the request.

   The following should be attached to the request:

   (a) statement of work

   (b) technical review, and

   (c) information identifying the individual(s) at CDC who should be notified when the negotiation is completed and the Assurance of Compliance approved by OPRR.

   For applications involving human participants from (1) foreign/international organizations and their foreign subcontractors who are conducting research involving human participants and (2) domestic institutions (with or without MPAs) who are subcontracting with a foreign/international organization that is participating in the research, the Contracts Branch must submit the following information to the Deputy ADS:

   1. PGO contact's name, title, telephone number, and mailstop;

   2. applicant organization's name, address, telephone number for the individual who signed the application, and the contract number;

   3. names and locations of all participating organizations;

   4. clear indication for applicant and each participating organization as to whether it has a MPA;

5. project title and projected budget period start date;

6. contract number; and

7. name, telephone number, and mailstop for the CDC Official.

The Deputy ADS will inform the Contracts Branch if any participating organizations already have Assurances of Compliance on record and provide the Assurance of Compliance numbers. If there is no Assurance of Compliance on record, the Deputy ADS will request it, and send a copy of the request to PGO. It will be the responsibility of the Contracts Branch to include the restriction provision into any contract for which an Assurance of Compliance is not on file.

During the month of September, when there is insufficient time to obtain the SPA before the award must be made to meet CDC's award deadlines, OPRR has agreed to allow awards with restrictions (language for the restriction provided by OPRR) on the use of funds for research involving humans.

Where the research will be conducted by cooperating institutions, all of the cooperating institutions must have Assurances of Compliance on file with OPRR.

Before a year has elapsed between the IRB approval date certified on the *Optional Form 310* and the anticipated award date, PGO requires IRB re-review and certification on a validly dated *Optional Form 310* prior to award.

Tracking CDC IRB Reviews

In some cases CDC scientists will function as investigators for some contracts. Under the Federal Regulations, each cooperating institution in a research project is responsible for reviewing the research. For those contracts, task orders, or purchase orders in which there are CDC coinvestigators, CDC is defined as one of the cooperating institutions and must review the research project just as the awardee and other participating organizations (e.g., subcontractors) must do. PGO needs to track initial and annual CDC, awardee, and other organization IRB reviews. CDC coinvestigators should send copies of their CDC IRB approval memos to the Contract Officer.

The following procedures will be implemented:
At the time of award, the Contracts Branch will verify with the CIO whether CDC investigators will be involved and whether the CDC IRB has reviewed and approved the protocol. If an exemption, according to 45 CFR 46.101, is claimed on the *Human Subjects Research Tracking Form* by the CIO, PGO will promptly forward the form to the Deputy ADS for concurrence. In addition to the standard language pertaining to research involving human participants, the contract will contain the following language when CDC investigators are to be involved as investigators and the CDC IRB has not met prior to award:

“Notice of Restricted Award Pending CDC Institutional Review Board (IRB) Approval -
It has been determined that this requirement will involve participation by CDC investigators in the

research activities; therefore, the CDC IRB is required to approve the protocol prior to beginning any tasks or using Federal funds that involve human subjects. Once the CDC IRB approval of the protocol is rendered, the Contract Officer will provide written notification removing the award restriction."

Noncompliance

Noncompliance by an Investigator

Common lapses in investigator compliance include unreported changes in protocols, misuse or nonuse of the informed consent document, and failure to submit protocols to the IRB in a timely fashion. Problems such as these are often caused by communication difficulties. With investigator goodwill, these cases can be resolved by the IRB without jeopardizing the welfare of research participants. Occasionally, an investigator will either avoid or ignore an IRB review. Such cases present a more serious challenge to the IRB and to the institution. Regardless of investigator intent, unapproved research involving human participants places those participants at an unacceptable risk. When unapproved research is discovered, the IRB and CDC will act promptly to halt the research, assure remedial action regarding any breach of regulatory or institutional human subject protection requirements, and address the question of the investigator's fitness to conduct human subject research. In addition, any serious or continuing noncompliance with the Federal Regulations will be reported to OPRR.

Noncompliance by an IRB

IRB noncompliance occurs whenever the IRB deviates from the duties imposed upon it by the Federal Regulations. Such deviations include the inadequate review of research protocols by failing to ensure that the consent document and process provide sufficient information to allow prospective participants to make an informed decision whether to participate in the research; failing to ensure that the research design includes adequate monitoring of the data and any additional safeguards necessary to protect the welfare of particularly vulnerable participants; and failing to conduct continuing review of research at intervals appropriate to the degree of risk. IRBs also breach their regulatory responsibilities by failing to maintain adequate records of IRB business and to hold their meetings with a majority of members present, including a nonscientific member. A demonstrated inability to carry out IRB responsibilities in accordance with the Federal Regulations can be cause for the suspension or withdrawal of CDC’s MPA.

Appendix I

CDC Human Subjects & IRB Staff

CDC Human Subjects & IRB Staff

http://intranet.cdc.gov/od/ads/hsr2.htm

Atlanta

FAX: 404-639-7341

Marjorie Speers, Ph.D. (404-639-7260; mas4@cdc.gov)
Deputy Associate Director for Science

Sheila Franklin (404-639-7260; sff1@cdc.gov)
Secretary - Sheila logs in all new protocols, amendments and continuation requests; she prepares the official protocol folders and creates the index cards which track activities conducted re: the current submission. Sheila attaches the appropriate checklists for informed consent and for vulnerable populations to the submitted copies, and she forwards the folder to **Virginia Talley;**

Virginia Talley (manages mailbox " Assurances-Human Subjects/OD"; 404-639-7621; vlt0@cdc.gov
Program Specialist - Virginia reviews protocol submissions for domestic and international assurance issues and maintains the tracking system of all official correspondence re: assurances. She notifies investigators that they need assurances on their protocols, assists them in obtaining SPAs, CPAs and other documentation of assurances that collaborating institutions are in compliance with OPRR requirements, and notifies them when all assurance issues are resolved. Virginia also negotiates and monitors cooperative amendments with other institutions' IRBs. When Virginia has documented the protocol's assurance status and entered it into her tracking system, she forwards the submission to **Mark Long;**

Mark Long (404-639-7098; msl1@cdc.gov)
Human Subjects Manager - Mark manages the day-to-day operations of the Human Subjects Office; he reviews all new protocols, amendments and continuations for coherence, completeness and compliance with the requirements in 45 CFR 46. Based on the results of his "triage" process, Mark informs investigators and CIO contacts of any additional clarification, documentation or other materials that must be submitted before their submission will be assigned to an IRB. He determines each protocol's eligibility for expedited review, and in consultation with **Marjorie Speers**, evaluates requests for exemption from IRB review and use of other institutions' IRBs. He attends all IRB meetings and advises the boards on procedural requirements for approval outlined in 45 CFR 46. Mark manages the IRBs' workloads and works with the chairs and members to ensure timely and thorough review of protocol submissions. In consultation with the IRB chairs and co-chairs, Mark assigns protocols for expedited and full-board reviews. He also handles urgent requests, complaints and negotiations between the IRBs and investigators. When the IRB has reviewed the protocol, a written report is sent to **IRB Reports (Pam Galusha);**

Pam Galusha (manages mailbox "IRB Reports-OD"; 404-639-7245; pkg0@cdc.gov)
Program Specialist - Pam advises investigators and IRB members on the wording of various

reports, responses, protocols and other study documents. Ms. Galusha prepares the weekly IRB agendas and sends relevant materials to the Boards; she also records the proceedings of the four Atlanta-based IRBs and the NCHS IRB, prompting the chairs and members to address procedural requirements defined in 45 CFR 46. Pam finalizes draft IRB reports from the reviewers and chairs and forwards them to investigators and CIO contacts, ccing the **Human Subjects Review-OD mailbox (Athena Carter);**

Athena Carter (manages mailbox "Human Subjects Review-OD"; 404-639-7245; awc1@cdc.gov)
Human Subjects Specialist - Athena is cc:'d on every HSO communication between the IRBs and CIOs. She also receives e-mailed IRB submissions from the CIOs and forwards them to Sheila Franklin for logging into the review process. Ms. Carter monitors the progression of protocols through the IRB review process, notates the index cards, updates the active protocol database (log), and maintains the official folders by filing all reports, investigator responses, and other IRB actions in the official folders. She interacts daily with the IRB chairs and primary reviewers, checking progress, forwarding investigators' responses. As a result, Athena is uniquely positioned to be the focal point for communications through this office; therefore, she answers all but the most unique or emergent status requests. Ms. Carter also manages the "Reminder" system that notifies investigators and CIO contacts of the need for annual continuing review of active protocols. Perhaps most importantly to investigators, Athena prepares and transmits IRB approval memos.

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Appendix II

Waiver Language Examples

IRB "Boilerplate" Language for Alteration of Informed Consent Process

(for use with IRB minutes, but could be "tweaked" for use in reports)

1. For waiver of 45 CFR 46.116(a)(4) (the alternative procedures required element):

   In accordance with 45 CFR 46.116(d), the Board voted to approve (?-?) an alteration of the informed consent process by waiving the required element of informed consent described in 45 CFR 46.116(a)(4) regarding appropriate alternative procedures that may be available to participants. The Board determined that the study would pose no greater than minimal risk to participants and that omission of this required element from the consent process would not adversely affect the rights or welfare of the subjects. In fact, for this type of research, the Board determined that the only appropriate alternative available to the subject would be to not participate in the study. Members felt that including such a statement could adversely affect the welfare of subjects by causing confusion and unnecessary concern, and, although investigators could simply include a statement to the effect that the "only alternative is to not participate," it seemed illogical to members, and they believed it could possibly jeopardize the credibility of the study. The Board, therefore, determined that it was not practicable to include the statement. The Board also decided that the fourth criterion for altering the informed consent process did not apply to this situation.

2. For waiver of 45 CFR 46.116(a)(7) (the research-related injury contact required element):

   In accordance with 45 CFR 46.116(d), the Board voted to approve (?-?) an alteration of the informed consent process by waiving the required element of informed consent described in 45 CFR 46.116(a)(7) regarding the inclusion of a contact person for research-related injury. The Board determined that the study would pose no greater than minimal risk to participants and that omission of this required element from the consent process would not adversely affect the rights or welfare of the subjects. The Board noted that participants are provided with information about whom to contact if they have questions about the research or if they have questions about their rights as research subjects. However, for this type of research, the Board determined that including such a statement could adversely affect the welfare of subjects by raising unnecessary concern about physical or other injury that would not occur. Members felt that although investigators could simply include a contact person for research-related injury, it seemed illogical to members, they believed it could possibly jeopardize the credibility of the study, and they felt it may be more harmful than beneficial to subjects. The Board, therefore, determined that it was not practicable to include the statement. The Board also decided that the fourth criterion for altering the informed consent process did not apply to this situation.

3. For waiver of 45 CFR 46.116(a)(8) (the "no penalty or loss of benefits" required element):

   In accordance with 45 CFR 46.116(d), the Board voted to approve (?-?) an alteration of the

informed consent process by waiving the required element of informed consent described in 45 CFR 46.116(a)(8) regarding including the statement that subjects may refuse to participate or may discontinue participation with no penalty or loss of benefits to which the subject is otherwise entitled. The Board determined that the study would pose no greater than minimal risk to participants and that omission of this required element from the consent process would not adversely affect the rights or welfare of the subjects. The Board felt that for this type research, a statement regarding "loss of benefits" was not relevant. In fact, the Board has been apprized that in some past situations, including this statement has led subjects to believe that the federal government is interfering with their benefits, resulting in mistrust of those involved in the study. The Board, therefore, determined that it was not practicable to include the statement. The Board also decided that the fourth criterion for altering the informed consent process did not apply to this situation.

Appendix III

IRB Reports

Report of CDC IRB “”
CDC Protocol #____, “”
(Date)

General Comments and IRB Actions

IRB “” has reviewed the request for approval of (new/amendment/continuation) and determined it to be a (no greater than minimal risk/greater than minimal risk) study. Upon receipt of satisfactory responses to the following issues and concerns and upon receipt of clean copies of the revised protocol/consent form/assent form/questionnaire, the IRB will approve the (protocol/amendment/continuation).

Protocol Issues

Response Required, Action Required

Response Required, Action Optional

Of Note (for information only; no response or action required)

Consent Form Issues

Response Required, Action Required

Response Required, Action Optional

Of Note (for information only; no response or action required)

Addenda Issues (Scripts, questionnaires, brochures, etc.)

Response Required, Action Required

Response Required, Action Optional

Of Note (for information only; no response or action required)

End of Report

Guidelines for Interpreting and Responding to CDC IRB Reports

The IRB report outlines the issues and concerns of the IRB in the attached format and is forwarded to investigators from the IRB Reports - OD electronic mailbox, or, for NCID investigators, from Susan Stokes or Steve Ostroff in NCID/OD. Responses to IRB reports should be forwarded to the Human Subjects Review - OD electronic mailbox; however, for NCID employees, responses to IRB reports should be forwarded to Susan Stokes or Steve Ostroff.

To facilitate the IRB's review of investigators' responses to reports, the Human Subjects Office requests that investigators copy the report and insert the highlighted (preferably redlined, boldfaced, or italicized) text of the responses after each item. If investigators revise the protocol, consent forms, or other related documents, they should provide a copy that has strikeout to denote deletions and highlight (redline, boldface, or italics) to indicate any new text that has been added. Clean copies of revised protocols, consent forms, or other related documents should also be forwarded with the response. Pages should be consecutively numbered (as should all documents submitted for IRB review) to also facilitate review of the response and to ensure that the response is thoroughly and fairly reviewed.

The first section of the report, General Comments and IRB Actions, tells the investigator exactly what action was taken by the IRB. The remainder of the report is divided into three categories that address (1) protocol issues, (2) consent form issues, and (3) addenda issues (scripts, questionnaires, brochures, etc.). These categories are further subdivided as follows:

Response Required, Action Required. These are issues for which the IRB requires (in accordance with the federal regulations) that investigators provide a written response and that they make the necessary revisions to the protocol, consent form, or other related documents before the protocol can be approved. If necessary, the IRB will include an explanation as to how the requested changes relate to the protection of human subjects, provide guidance, and/or provide examples of suggested revisions. If the required action cannot be carried out or investigators do not wish to make the suggested changes, investigators must submit an acceptable explanation and/or justification in their response to the IRB.

Response Required, Action Optional. These are issues for which the IRB requires that investigators provide a written response, but for which approval is not contingent upon investigators accepting the suggested changes. Investigators' responses should, however, indicate to the IRB that they have considered the scientific and ethical impact and consequences of the issues.

Of Note (for information only; no response or action required). These issues include minor comments, notes of grammatical or typographical errors, etc. Although the IRB is not requiring any response or action on the part of the investigators, these are issues that if clarified may improve the IRB's understanding of the study's purpose and/or design or may

clarify issues to the participants.

Clear and constructive communication between CDC's IRBs, the Human Subjects Office, and investigators will greatly facilitate timely reviews of protocols and will assist CDC staff in conducting research studies that are scientifically meaningful and ethically sound.

For additional information and/or assistance in interpreting and responding to IRB reports, investigators may contact:

1. The CIO Human Subjects Contact (the Human Subjects Office can provide this point-of-contact if investigators do not know who occupies this position in their CIO), or

2. Mark Long or Pam Galusha in the Human Subjects Office at:

Mr. Mark Long
Human Subjects Manager
OD/ADS (Mailstop D50)
Building 16, Room 4329
(404) 639-7098
(404) 639-7341 (fax)
msl1@cdc.gov

Ms. Pam Galusha
Program Specialist
OD/ADS (Mailstop D50)
Building 16, Room 4315
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Appendix IV

Checklists

Review Date: _____

Informed Consent Checklist for Protocol # _____

CDC holds a Multiple Project Assurance with the Office for Protection from Research Risks (OPRR), NIH, whereby CDC agrees to abide by the requirements of Title 45 Code of Federal Regulations for the Protection of Human Subjects (45 CFR 46).

Section 116 (§46.116) of the federal regulations gives the general requirements for informed consent. The section reads, in part, "...no investigator may involve a human being as a subject in research covered by this policy unless the investigator has obtained the legally effective informed consent of the subject..."

The purpose of this checklist is to aid you in your evaluation of the informed consent documents accompanying each protocol to assure that those required elements are included. Please use the blocks to make notes or simply check that the basic requirement has been satisfactorily addressed.

All consent document must address the following three principles:

Requirement	**45 CFR 46.116**	**Consent form**
Voluntariness	A. "An investigator shall seek...consent only under circumstances that provide the prospective subject...sufficient opportunity to consider whether or not to participate..."	
	B. "...and minimize the possibility of coercion or undue influence."	
Comprehension	"The information...given to the subject...shall be in language understandable to the subject..." The reading grade level and method (SMOG, Fry, Flesch-Kincaid) used to determine the reading grade level must be specified.	Grade level: _____ SMOG: _____ Fry: _____ Flesch-Kincaid: _____
Coercion	No informed consent... may include any exculpatory language through which the subject...is made to waive...any of the subject's legal rights, or releases the investigator, the sponsor or the institution ...from liability for negligence.	

Minimal Risk

The Federal Regulations divide research into that which is minimal or not greater than minimal risk to the participant and that which is greater than minimal risk. The definition of minimal risk given in §46.102(I) reads as follows:

"Minimal risk means that the ***probability*** and ***magnitude*** of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."

Level of Risk for this protocol (please insert "minimal" or "greater than minimal"):

_____

Required Elements of Informed Consent

The Federal Regulations at §46.116 describes eight elements required in each consent document. Element number six is only required if the research is determined to be greater than minimal risk. This section also lists an additional six elements that "When appropriate...shall also be provided to each subject."

Please use the following determination key when evaluating each element:

Y = appropriately included in the consent form
N/A = element not required for this study (IRB must waive and document)
M = element missing (the consent form must be revised to include this element or the requirement must be waived by the IRB)
I = incomplete or problematic

Element	45 CFR 46.116(a)	Consent form
1	A. a statement that the study involves research	
	B. an explanation of the purposes of the research	
	C. the expected duration of the subject's participation	
	D. a description of the procedures to be followed	
	E. identification of any procedures which are experimental	
2	a description of any reasonably foreseeable risks or discomforts to the subject	
3	a description of any benefits to the subject or to others which may reasonably be expected from the research	
4	a disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject	
5	a statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained	
6	A. an explanation as to whether any compensation is available if injury occurs	
	B. an explanation as to whether any medical treatments are available if injury occurs, and, if so	
	C. what they consist of or where further information may be obtained	
7	A. an explanation of whom to contact for answers to pertinent questions about the research	
	B. an explanation of whom to contact for answers to pertinent questions about the research subjects' rights	

Element	45 CFR 46.116(a)	Consent form
	C. whom to contact in the event of a research-related injury to the subject	

Element	45 CFR 46.116(a)	Consent form
8	A. a statement that participation is voluntary	
	B. refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled	
	C. the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled	
Additional elements (45 CFR 46.116(b) of informed consent (when appropriate, one or more of the following elements of information shall also be provided to each subject):		
1	a statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable	
2	anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent	
3	any additional costs to the subject that may result from participation in the research	
4	A. the consequences of a subject's decision to withdraw from the research	
	B. procedures for orderly termination of participation by the subject	
5	a statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject	
6	the approximated number of subjects involved in the study	

Review Date: _____

Additional DHHS Protections Pertaining to Research, Development, and Related Activities Involving Fetuses, Pregnant Women, and Human In Vitro Fertilization

Checklist for Protocol # _____

The purpose of this checklist is to aid you in your evaluation of CDC research involving fetuses, pregnant women, and human in vitro fertilization. In addition to the responsibilities of the IRB under Subpart A, the IRB shall carry out the following ***additional duties*** when research involves fetuses, pregnant women, and human in vitro fertilization. However, if pregnant women and fetuses are ***NOT*** the target of the research, Subpart B does not apply.

Minimal Risk

The Federal Regulations divide research into that which is minimal or not greater than minimal risk to the participant and that which is greater than minimal risk. The definition of minimal risk given in §46.102(i) reads as follows:

"Minimal risk means that the ***probability*** and ***magnitude*** of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."

Level of Risk for this protocol (please insert "minimal" or "greater than minimal"):

_____

_____

Please use the following determination key when evaluating research involving fetuses, pregnant women, and human in vitro fertilization to ensure that the ***additional safeguard*** has been satisfactorily addressed:

Y = adequately addressed in protocol
M = missing in protocol
I = incomplete or problematic in protocol

Additional Safeguard	**45 CFR 46 Subpart "B" § 46.205**	**Notes**
Selection	"determine that adequate consideration has been given to the manner in which potential subjects will be selected..."	
Informed Consent	"...adequate provision has been made...for monitoring the actual informed consent process. For example:	
	"overseeing the actual process by which individual consents required ...are secured either by approving induction of each individual ...or verify...that approved procedures for induction...are being followed..."	
	"monitoring the progress...and intervening as necessary through such steps as visits to the ...site and continuing evaluation to determine if any unanticipated risks have arisen..."	
Animal Studies	"...appropriate studies on animals and nonpregnant individuals have been completed."	
Risk	"except where the purpose...is to meet the health needs of the mother or...fetus, the risk to the fetus is minimal and, in all cases, is the least possible risk for achieving the objectives..."	
Pregnancy Termination/Fetal Viability	"individuals engaged...will have no part in any decisions as to the timing, method, and procedures used to terminate the pregnancy..."	
	"individuals engaged...will have no part in determining the viability of the fetus at the termination of the pregnancy; and..."	
	"no procedural changes which may cause greater than minimal risk to the fetus or the pregnant women will be introduced...for terminating the pregnancy solely in the interest of the activity,	
	"No inducements, monetary or otherwise, may be offered to terminate pregnancy for purposes of this activity.."	

Activities directed toward pregnant women as subjects:

Additional Safeguard	§ 46.207	Notes
Purpose	"...is to meet the health needs of the mother and the fetus will be placed at risk only to the minimum extent necessary to meet such needs or...	
Risk	the risk to the fetus is minimal."	
Competency	"...the mother and father are legally competent and...	
Informed Consent	have given their informed consent after having been fully informed regarding possible impact on the fetus (both mother's and father's signature blocks), except...	
Provisions if Father's Signature Not Secured	"...the father's informed consent need not be secured if: (1) the purpose...is to meet the health needs of the mother; (2) his identity or whereabouts cannot reasonably be ascertained; (3) he is not reasonably available; or (4) the pregnancy resulted from rape".	

Activities directed toward fetuses in utero as subjects:

Additional Safeguard	§ 46.208	Notes
Purpose	"...is to meet the health needs of the particular fetus and...	
Risk	...the fetus will be placed at risk only to the minimum extent necessary to meet such needs, or	
	the risk to the fetus imposed by the research is minimal and the purpose...is the development of important biomedical knowledge which cannot be obtained by other means."	
Competency	"...the mother and father are legally competent and...	
Informed Consent	have given their informed consent after having been fully informed regarding possible impact on the fetus (both mother's and father's signature blocks), except...	
Provisions if Father's Signature Not Secured	"...the father's informed consent need not be secured if: (1) the purpose...is to meet the health needs of the mother; (2) his identity or whereabouts cannot reasonably be ascertained; (3) he is not reasonably available; or (4) the pregnancy resulted from rape".	

Review Date: _____

Additional DHHS protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects

Checklist for Protocol # _____

The purpose of this checklist is to aid you in your evaluation of CDC research involving prisoners inasmuch as prisoners may be under constraints because of their incarceration which could affect their ability to make a truly voluntary and uncoerced decision whether or not to participate as subjects in research. These requirements are in addition to those imposed under other subparts of the Federal Regulation.

Minimal Risk

The Federal Regulations divide research into that which is minimal or not greater than minimal risk to the participant and that which is greater than minimal risk. The definition of minimal risk for research involving prisoners is given in §46.303(d), which reads as follows:

"Minimal risk is the ***probability*** and ***magnitude*** of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of health persons."

Level of Risk for this protocol (please insert "minimal" or "greater than minimal"):

_____

An IRB can only approve research that falls into one of the following four categories (complete/check one only):

Category	45 CFR 46 Subpart "C" § 46.306	Notes
Cause and Effect	"study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided...	
	...that the study presents no more than minimal risk AND	
	no more than inconvenience to the subjects."	
Institutional Structures	"study of prisons as institutional structures or of prisoners as incarcerated persons, provided...	
	...that the study presents no more than minimal risk AND	
	no more than inconvenience to the subjects."	
Conditions Affecting Prisoners as Class	"research on conditions particularly affecting prisoners as a class (e.g., vaccine trials ...on hepatitis which is much more prevalent in prisons; and research on social and psychological problems such as alcoholism, drug addition, and sexual assaults)..."	

Category	45 CFR 46 Subpart "C" § 46.306	Notes
Improving Health and Well-being	"research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject."	

Please use the following determination key when evaluating research involving prisoners to ensure that the ***additional safeguard*** has been satisfactorily addressed:

Y = adequately addressed in protocol
M = missing in protocol
I = incomplete or problematic in protocol

Additional Safeguard	§ 46.305	Notes
Legal	"research...limited by applicable State or local law."	
Controls	"Unless the PI provides to the Board justification in writing for following some other procedures, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed..."	
Advantages	"any possible advantages accruing to the prisoner through his or her participation..., when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in prison, are not of such a magnitude that his or her ability to weigh the risks...against the value of such advantages in the limited choice environment of the prison is impaired;	
Risks	...are commensurate with risks that would be accepted by nonprisoner volunteers;	
Selection	"procedures...are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners.	
Comprehension	"...information is presented in language which is understandable..."	
Parole	"adequate assurance exists that parole boards will not take into account a prisoner's participation...in making decisions regarding parole, and each prisoner is clearly informed in advance that participation...will have no effect on his or her parole..."	
Follow-up	"where the Board finds there may be a need for follow-up examination or care...after...participation, adequate provision has been made for such examination or care, taking into account the varying lengths of individual prisoners' sentences, and for informing participants of this fact."	

Review Date: _____

Additional DHHS Protections for Children Involved as Subjects in Research

Checklist for Protocol # _____

The purpose of this checklist is to aid you in your evaluation of CDC research involving children. In addition to other responsibilities assigned to IRBs..., each IRB shall review and approve only research which satisfies the conditions of all applicable sections of the Federal Regulation dealing with children.

Minimal Risk

The Federal Regulations divide research into that which is minimal or not greater than minimal risk to the participant and that which is greater than minimal risk. The definition of minimal risk given in §46.102(I) reads as follows:

"Minimal risk means that the ***probability*** and ***magnitude*** of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."

Level of Risk for this protocol (please insert "minimal" or "greater than minimal"):

_____

An IRB can only approve research that falls into one of the following four categories (complete/check one only):

Category	46 CFR 46 Subpart "D"	Notes
Not Involving Greater than Minimal Risk 45 CFR 46.404	"...only if...IRB finds that adequate provisions...made for soliciting...assent of the children AND...	
	...the permission of their parents or guardians... (one parent may give permission)"	
Greater than Minimal Risk but...Prospect of Direct Benefit to the Individual Subjects or by a Monitoring Procedure that is Likely to Contribute to the Subject's Well-being 45 CFR 46.405	"...risk...justified by...anticipated benefit to...subjects AND...	
	...relation of... anticipated benefit to...risk is at least as favorable... as that presented by available alternative approaches; AND...	
	...adequate provisions...made for soliciting...assent of the children...AND...	
	...the permission of their parents or guardians (one parent may give permission)."	

Category	46 CFR 46 Subpart "D"	Notes
Greater than Minimal Risk and No... Direct Benefit to Individual Subjects, but Likely to Yield Generalizable Knowledge about...Subject's Disorder or Condition or...a Monitoring Procedure...Likely to Contribute to...Subject's Well-being *45 CFR 46.406*	"...risk represents a minor increase over minimal risk AND...	
	...intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in... actual or expected medical, dental, psychological, social, or educational situations; AND...	
	...intervention or procedure...likely to yield generalizable knowledge about...subjects' disorder or condition which is of vital importance for...understanding or amelioration of... subjects' disorder or condition; AND...	
	...adequate provisions are made for soliciting assent of the children AND...	
	...permission of their parents or guardians (both parents must give permission)."	
Not Otherwise Approvable which Presents...Opportunity to Understand, Prevent, or Alleviate...Serious Problem Affecting...Health or Welfare of Children *45 CFR 46.407*	*If you check this category, IRB should not approve without consulting the Human Subjects Office.*	

Children who are wards of the State or any other agency, institution, or entity can be included in research approved under §46.406 or §46.407 only if 45 CFR 46.409 applies.

Developing a Protocol

Quality of science is often improved when study objectives and methods are clearly thought through and described. A written protocol facilitates high quality science and is an invaluable tool to investigators as they develop and conduct studies.

Regardless of the scientific discipline in which the study is undertaken, the same scientific method is used. Further, while the scientific content will differ across studies, the general elements of the study protocol will be similar.

The Excellence in Science committee has developed a general protocol checklist and companion guide to assist scientists in preparing protocols. The checklist is intended as an aid in suggesting a format for writing protocols and in identifying issues that scientists should consider as they design the study.

With many scientific disciplines represented by CDC scientists, the checklist was developed to have utility in conducting laboratory and basic science studies, epidemiologic studies, and behavioral and social science studies employing a variety of study designs. In using the checklist, investigators should select the items that apply to their types of studies. It is unlikely that any protocol would include every item on the checklist.

A number of studies are conducted at CDC that are not classified as research or do not involve humans as participants. To make the checklist applicable to the widest range of studies, the general protocol checklist does not contain requisite protocol items for review by an institutional review board. A separate addendum checklist for Protection of Human Research Participants is included.

GENERAL PROTOCOL CHECKLIST

This checklist is intended as an aid in suggesting a format for writing protocols and in identifying issues that scientists should consider as they design a study or surveillance system. When using the checklist, investigators should select the items that apply to their specific project. It is not expected that every item on the checklist is applicable to each protocol for a study or surveillance system.

Section	Item	/
PROJECT OVERVIEW	Title	
	Protocol summary	
	Investigators & roles/collaborators & roles/funding sources	
INTRODUCTION	Literature review/current state of knowledge about project topic	
	Justification for study	
	Intended/potential use of study findings	
	Study design/locations	
	Objectives	
	Hypotheses or questions	
	General approach	
PROCEDURES/METHODS DESIGN	How study design or surveillance system addresses hypotheses and meets objectives	
	Audience and stakeholder participation	
	Cost benefit/prevention effectiveness	
	Study time line	
	Expeditious protocol review request	
PROCEDURES/METHODS STUDY POPULATION	Description and source of study population and catchment area	
	Case definitions	
	Participant inclusion criteria	
	Participant exclusion criteria	
	Justification of exclusion of any sub-segment of the population	
	Estimated number of participants	
	Sampling, including sample size and statistical power	
	Enrollment	
	Consent Process	

Section	Item	/
PROCEDURES/METHODS VARIABLES/INTERVENTIONS	Variables	
	Study instruments, including questionnaires, laboratory instruments and analytic tests	
	FDA Investigational New Drug (IND) or Investigational Device Exemption (IDE) information	
	Intervention or treatment	
	Outcomes and minimum meaningful differences	
	Training for all study personnel	
PROCEDURES/METHODS DATA HANDLING AND ANALYSIS	Data analysis plan, including statistical methodology and planned tables and figures	
	Data collection	
	Information management and analysis software	
	Data entry, editing and management, including handling data collection forms, different versions of data and data storage and disposition	
	Quality control/assurance	
	Handling results in the absence of a reference test	
	Measurement/estimation and adjustment for cross reactivity	
	Verifying independence of tests used to confirm results of new test being studied	
	Bias in data collection, measurement and analysis	
	Intermediate reviews and analyses	
	Limitations of study	
PROCEDURES/METHODS HANDLING OF UNEXPECTED OR ADVERSE EVENTS	Response to new or unexpected findings and to changes in the study environment	
	Identifying, managing and reporting adverse events	
	Emergency care	
PROCEDURES/METHODS DISSEMINATION, NOTIFICATION, AND REPORTING OF RESULTS	Notifying participants of their individual results	
	Notifying participants of study findings	
	Anticipated products or inventions resulting from the study and their use	
	Disseminating results to public	

Section	Item	/
REFERENCES		
APPENDIX MATERIALS	Data collection forms	
	Proposed tables and figures	
	Other relevant documents	

GUIDE FOR GENERAL PROTOCOL CHECKLIST

PROJECT OVERVIEW

***Title*:** Summarize the main idea under investigation. The title should be able to stand alone as an explanation of the study.

Protocol summary: Give a concise overview of the project. Describe the purpose of the study, including problem to be investigated and hypothesis(es) to be tested, the population, and the methods that will be used. Avoid the use of acronyms. Include the expected benefit of the study.

Investigators/collaborators/funding sources: Include the names and degrees of all investigators and their roles in the project. Note any conflict of interest for each investigator and acknowledge all funding sources.

INTRODUCTION

Literature review/current state of knowledge about project topic: Discuss relevant information about the subject of the project based on a review of the literature. In the Reference section, attach a bibliography of the sources used.

Justification for study: Explain the public health and scientific importance of the study. In the context of previous studies, describe the contribution this study will make.

Intended/potential use of study findings : Define the primary target audiences and discuss the expected applicability of study findings.

Study design/locations: Describe the study design and the locations where the study will be conducted.

Objectives: Clearly and concisely list the objectives that the project will address.

***Hypotheses or questions* :** List the clear and focused question(s) that the study will answer. State the type of hypothesis(es) that will be explored or tested.

General approach: Describe whether the approach used will be descriptive, exploratory (hypothesis-generating), confirmatory (hypothesis testing), or developmental (focused on corrective action).

PROCEDURES/METHODS

DESIGN

How study design or surveillance system addresses hypotheses and meets objectives: Explain the appropriateness of the study design to the project and to the questions and objectives previously outlined. Distinguish between procedures that are experimental and those that involve routine care. Identify specific design attributes that characterize the study design (e.g., cross-sectional survey, case/control, cohort, focus group, chart review, etc.) or surveillance system (e.g., description of the system as active or passive, defining reported cases as individual versus

aggregate and as laboratory confirmed or not).

Audience and stakeholder participation: Define the primary audiences for the project. Assess the major stakeholders and describe ways they can (and cannot) participate in the study. Explain the process by which those affected by the study can express their views, clarify their needs, and contribute to the project.

Cost benefit/prevention effectiveness: Describe how these measures will be addressed.

Study time line: Provide a calendar with estimated dates for implementing and completing key activities.

Expeditious protocol review: If appropriate, describe the need for an expeditious review of the protocol (e.g., because it is for an ongoing outbreak or emergency disaster).

STUDY POPULATION

***Description and source of study population and catchment area*:** Demographically and in terms of the specific public health conditions to be studied, define the population from which the participants, sample or surveillance subjects will be drawn and to what population inferences will be made.

Case definitions: Provide descriptions of illness, condition or health event which defines a study participant as having that condition.

***Participant inclusion criteria*:** Describe conditions or characteristics applicable to the identification and selection of participants in the study and the conditions necessary for eligible persons to be included.

Participant exclusion criteria: Describe characteristics that would disqualify otherwise eligible participants from the project.

Justification of exclusion of any sub-segment of the population: If a sub-population as defined by gender, race/ethnicity, or age is excluded, provide reasons. In accordance with CDC's policy for inclusion of women and minorities in research, state how these populations are included in the sponsoring CIO's overall program of research if excluded in this particular study.

***Estimated number of participants*:** State the estimated number of participants for the study. For a project establishing or using data from a surveillance system, this may include the expected number of reported cases per reporting period for epidemic and non-epidemic periods.

Sampling, including sample size and statistical power: Describe the sample (e.g., the sample will be one of convenience, a population-based representation or systematically chosen for some other purpose). State the sampling units and units of analysis. Estimate required sample sizes to answer questions and test statistical hypotheses (based on available information from pilot studies or previous reports). Include statistical power estimates. Explain the conditions under which sampling estimates would be revised. If group-level or aggregate information will be collected

(e.g., from focus groups), explain how the groups will be comprised, or what procedures will be followed to create appropriate groups.

Enrollment: Describe the manner in which potential participants will be contacted, screened, and registered in the study. Describe procedures for tracking the number of persons who withdraw from the study. Explain the procedures for assigning participants to different groups. Include a discussion of how departures from the intended enrollment procedures will be handled and documented.

Consent Process: Describe procedures for informing participants about study and methods and for obtaining consent.

VARIABLES/INTERVENTIONS

Variables: List and briefly describe the categories, topics, or domains of information to be explored and variables to be collected. Address consistency of definition of variables for data collected from multiple sources. Traditionally, for outbreak investigations, "time", "place" and "person" would be collected to construct the epidemiologic curve. Explain how the variables will be utilized and the process by which variables will be defined.

Study instruments, including questionnaires, laboratory instruments, and analytic tests: Describe strategies to elicit information, including specific techniques and study and laboratory instruments, and explain how they will be used. Describe the attributes of those strategies/ instruments as demonstrated in other studies, including appropriateness, validity and reliability within the particular study populations, sensitivity and specificity of instruments, how well they yield reproducible results and whether any controversial methods are being used. Include a discussion of how changes to the study instruments will be handled and documented.

FDA Investigational New Device (IND) or Investigational Device Exemption (IDE) information: If the study involves the use of an investigational new drug or investigation new device, provide the IND or IDE number and relevant information.

Intervention or treatment: Describe the types of interventions or treatments that will be tested in detail, including dosing, schedules of administration, etc.

Outcomes and minimum meaningful differences: List the possible results of exposure or intervention of interest in the study (i.e., the outcomes) and what clinical or epidemiologic differences in measurement of the outcomes are important to detect.

Training for all study personnel: Describe training, such as interviewer techniques, data collection and handling methods or informed consent, provided to study personnel. Address how inter-observer differences will be handled.

DATA HANDLING AND ANALYSIS

Data analysis plan, including statistical methodology and planned tables and figures: Describe the sampling methods, information collection procedures, methods to maximize response rates, test procedures and relevant statistical quantities (e.g., variance, confidence intervals and

power based on data from the study) in sufficient detail that the methods are reproducible. This includes calculation of relevant quantitative measures for tests and instruments, such as sensitivity and specificity. In outbreak investigations, it is common to employ an iterative process in the analysis (consisting of developing and testing hypotheses and planning and evaluating interventions) to identify the source of the outbreak and control it. For projects establishing or utilizing data from a surveillance system, this could include how and how often the surveillance system will be evaluated. Describe what tables and figures are planned to present study results.

Data collection: Describe data collection procedures, processes and documentation. For data emanating from a surveillance system, this would include frequency of reports.

Information management and analysis software: Provide the names of data entry, management and analysis software packages and computer programming languages to be used for the project.

Data entry, editing and management, including handling of data collection forms, different versions of data, and data storage and disposition: Describe the overall procedures for management of the data collected. Include in the description the process for entering and editing data. Describe how study materials, including questionnaires, statistical analyses, unique reagents, annotated notebooks, computer programs and other computerized information, whether used for publication or not, will be maintained to allow ready, future access for analysis and review. Document operating procedures for managing and accessing different versions of data sets. State who the data belong to and any rights to and limitations to access for any primary and secondary data analyses and publications. Document procedures regarding confidentiality of the data, including how confidentiality will be preserved during transmission, use and storage of the data and the names of persons or positions responsible for technical and administrative stewardship responsibilities. Document what the final disposition of records, data, computer files, and specimens will be, including location for any relevant information to be stored. Records must be stored in compliance with CIO or Agency guidelines.

***Quality control/assurance*:** Describe the steps that will ensure no unintended consequences that could affect the quality of the data. Those steps might include methods to capture all reported data exactly as received, assuring logical consistency among all parts of a record and ensuring that manipulation or transformation of the data (e.g from audio tape to transcribed text) produces no unintended changes, and verifying that statistical and arithmetic calculations are performed as proposed in the data analysis plan. For outbreak investigations, this would include verifying diagnosis and confirming the outbreak. Describe procedures for ongoing data quality monitoring to assure that information of appropriate depth, breadth, and specificity is collected and remains consistent within and among staff over time, and acceptable levels of such attributes as validity, reliability, reproducibility, sensitivity and specificity are achieved.

Handling results in the absence of a reference test: Describe how tests will be used and results interpreted in the absence of a referent test and/or consensus of multiple test results. Include how sensitivity and specificity are affected.

Measurement/estimation and adjustment for cross reactivity: Describe how cross reactivity will be measured, its potential effects on test results and how it will be accounted/adjusted for in

the analysis.

Verifying independence of tests used to confirm results of new test being studied: Describe process to validate results and use of new test, including verification of independence of tests or adjustments made for non-independence.

Bias in data collection, measurement and analysis: Describe the kinds of bias that may occur in collecting the data or in the measurement or analysis phases, and the steps that will be taken to avoid, minimize and compensate for the bias. Include factors in the study population or in study personnel that could bias results, as well as the steps that will be taken to assure valid self-reporting or recording of observations. Include any randomization and blinding procedures that will be used to eliminate/minimize bias by investigators, other study staff or participants (e.g., in selection of participants, allocation to treatment groups, providing/receiving treatment).

Intermediate reviews and analyses: Describe the ways that progress will be tracked and the study will be evaluated prior to assessing final results.

Limitations of study: Explain factors that might reduce the applicability of study results. Discuss potential weak points or criticisms of the study, including alternative methods.

HANDLING OF UNEXPECTED OR ADVERSE EVENTS

Response to new or unexpected findings and to changes in the study environment: Describe procedures for identifying and handling new or unexpected findings, and responding to changes in the study environment.

Identifying, managing, and reporting adverse events: Describe the types of adverse events that might be encountered and how study personnel will be trained to react. Describe methods that will be used to track adverse reactions and their potential impact on the study.

Emergency care: Explain the actions that would be taken in the event that an emergency develops during a study participant's involvement in the research.

DISSEMINATION, NOTIFICATION, AND REPORTING OF RESULTS

Notifying participants of their individual results: Describe the process used to notify study participants of their results, including those of immediate importance. Include precipitating circumstances and whether or not counselors will be used.

Notifying participants of study findings: Explain whether the participant will be offered the option of receiving overall study findings and the form they will take.

Anticipated products or inventions resulting from the study and their use: List any products, including inventions, derived from the study, and how those will be used.

Disseminating results to public: Define effective communication channels and best formats for presenting information that will be used to disseminate project results to specific target audiences.

REFERENCES

List bibliographic references used to create and delimit all aspects of the study.

APPENDIX MATERIALS

Data collection forms: Include any forms or documents used to collect data or from which data are abstracted. Examples of these are questionnaires, medical records and other abstraction forms.

Proposed Tables and figures: Provide table shells and examples of figures for presentation of data and study results.

Other relevant documents: Include any other relevant supplementary materials.

SUPPLEMENTAL PROTOCOL CHECKLIST
PROTECTION OF HUMAN RESEARCH PARTICIPANTS

Section	Notes	/
RISKS	Physical	
	Social	
	Psychological	
METHODS TO MINIMIZE RISKS		
ANTICIPATED BENEFITS		
RISK/BENEFIT RATIO		
VULNERABLE POPULATIONS	Pregnant Women, Fetuses, *in vitro Fertilization*	
	Prisoners	
	Children	
IMPLEMENTATION/ DOCUMENTATION OF INFORMED CONSENT		
JUSTIFICATION FOR WAIVER/ALTERATION OF INFORMED CONSENT		
JUSTIFICATION FOR WAIVER/ALTERATION OF *DOCUMENTATION* OF INFORMED CONSENT		
IMPLEMENTATION/ DOCUMENTATION OF ASSENT (CHILDREN)		
IMPLEMENTATION/ DOCUMENTATION OF PARENTS'/GUARDIANS' PERMISSION		

Section	Notes	/
PROTECTION OF PRIVACY AND CONFIDENTIALITY	Privacy of Individual	
	Confidentiality of Data	
ASSURANCE/ CERTIFICATE OF CONFIDENTIALITY	Assurance of Confidentiality (308(d) PHS Act; protects both individuals and institutions)	
	Certificate of Confidentiality (301(d) PHS Act; protects only individuals	
EXTRA COSTS		
REIMBURSEMENTS/ INCENTIVES		
APPENDIX MATERIAL (RELEVANT SUPPLEMENTARY MATERIALS)		

SUPPLEMENTAL GUIDE FOR PROTOCOL CHECKLIST
PROTECTION OF HUMAN RESEARCH PARTICIPANTS

Description of risks (physical, social, psychological) to the individual or group. Include methods to minimize risks: Define the nature, magnitude, probability, and duration of potential harms that a person may receive by participating in this research. Describe steps that have been taken to minimize risks, including the use of sound research design and by using procedures already being performed on the participant or other routine procedures that will be provided to the participant.

***Description of anticipated benefits to the research participant*:** Discuss benefits to research participants resulting from the research. Describe the steps that have been, or will be, taken to maximize benefits.

Description of the potential risks to anticipated benefit ratio: Justify that the potential risk are reasonable in relation to anticipated benefits and the importance of the knowledge that may reasonably be expected to result from the research.

Justification for involving vulnerable participant populations: If study participants include a special or vulnerable population, such as children, prisoners or mentally incompetent, provide justification for their use in terms of the purpose of the research.

Procedures for implementing and documenting informed consent: Describe procedures for informing participants and methods to obtain and document consent.

Justification for waiver or alteration of informed consent: If informed consent will not be obtained or will be altered, describe the justification for waiver. The justification must address the four criteria for waiving or altering consent: 1) the research involves no more than minimal risk to the participants, 2) the waiver or alternation will not adversely affect the rights and welfare of the participants, 3) the research could not practicably be carried out without the waiver or alteration, and 4) whenever appropriate, the participants will be provided with additional pertinent information after participation.

Justification for waiver of documentation of informed consent: If written informed consent will not be obtained, provide justification for obtaining consent through other means. The justification must address one of the two criteria for waiving documentation: 1) that the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality or 2) that the research presents no more than minimal risk of harm to participants and involves no procedures for which written consent is normally required outside of the research context. If the first criterion is used, describe the procedures to ensure that participants' wishes regarding documentation linking them to the research will be ascertained and honored.

Description of procedures for implementing and documenting the assent process of children: Describe procedures for informing children and methods to document assent.

Description of procedures for implementing and documenting parents' or guardians' permission: Describe procedures for informing participants and methods to document parental permission.

***Provisions for protecting privacy/confidentiality*:** Explain provisions for protecting study participants from being identified either directly or indirectly. If for any reason data identifying subjects will be published or released to persons outside of the project, explain why this is necessary.

Statement about need or lack of need for assurance or certificate of confidentiality: This refers to formal assurances and certificates of confidentiality.

Statement of extra costs to participants due to involvement in the study: Self explanatory.

Description and justification of reimbursements or incentives that will be used: Self explanatory.

If the study involves special populations, such as pregnant women, fetuses, prisoners, children or human in vitro fertilization, include a section that specifically addresses the requirements of HHS regulations 45 CFR 46.

1. ***If fetuses are included, see Subpart B of 45 CFR 46.***
2. ***If pregnant women are participants, see Subpart B of 45 CFR 46.***
3. ***If human in vitro fertilization is used, see Subpart B of 45 CFR 46.***
4. ***If prisoners are participants, see Subpart C of 45 CFR 46.***
5. ***If children are participants, see Subpart D of 45 CFR 46.***

APPENDIX MATERIALS

Include all relevant supplementary materials. All materials for use by participants must be written in lay language.

Announcements/advertisements, notification letters, videos, scripts, other information for participants: Recruiting literature should include the purpose of the research and the selection criteria for inclusion in the study, a straightforward and simple description of the study, potential risks and benefits, method of compensation for time and inconvenience, the location of the research, sponsoring agencies, the person to contact for further information, an estimate of the time per session and total time of participation.

Data collection forms
Questionnaires, interview schedules, observation plans, focus group discussion guides, etc.
Coding guidelines and definitions of themes/variables
Medical records and / or other abstraction forms
Request and authorization for release of medical records
Manuals for training study personnel.
Consent and assent forms

Appendix V

Adverse Events Forms

CDC Human Subjects Adverse Event Report

(To Be Filled Out By Lead CDC Investigator)

An adverse event (AE) is defined as a physical injury to human research participants. Serious events (i.e., life threatening) should be reported to the IRB within 24 hours. Less serious injuries must be reported to the IRB within two weeks of their occurrence.

Please complete and sign this form. Submit to the Human Subjects Manager, Mark Long, at Mailstop D-50. Following review by the IRB, the IRB Chair will notify the Deputy ADS, who will notify OPRR in writing of the event and the corrective actions taken.

CDC Investigator: _____

Protocol Number: _____

Participant's I.D. (if available): _____

Date of Event: _____

Date First Known to You: _____

Name of Drug, Device or Procedure: _____

Describe in detail the nature of the AE and timing of the event (attach addendum if necessary):

The likelihood the event was caused by the study is:

_____ Probable _____ Possible _____ Unlikely _____ Definitely unrelated

Impact on participant (Check all that apply):

_____ Participant died
_____ Required follow-up treatment
_____ Resulted in prolonged hospitalization
_____ Participant remains on study
_____ Resulted in disability
_____ Required first aid
_____ Attention beyond first aid

Did investigator report this AE to? (Check all that apply)

_____ Co-investigator _____ FDA _____ Data Safety Monitoring Board

Describe corrective action taken by study investigator: (Check all that apply)
_____ Stop enrollment of new participants
_____ Halt the study
_____ Change data management/ coding procedures
_____ Form committee to review procedures
_____ Other (Please Comment)

Does this event require revision to the (YES or NO):	_____ Protocol	_____ Consent Form
If yes, please submit amendment (CDC form 1252), revised protocol and consent form.		
Signature of lead CDC investigator: _____ **Date:** _____		
Printed name of lead CDC investigator: _____ **Phone:** _____		

Approvals (Signature and Position Title)	**Date:**	**Remarks:**
Branch Chief:		
Division Director:		
CIO HSC:		

CDC Human Subjects Unanticipated Problem/Breaches of Protocol Report
(To Be Filled Out By Lead CDC Investigator)

Breaches in protocol and unanticipated problems include, but are not limited to, breakdowns in the consent process, violations of confidentiality of the data, and complaints by participants. Serious events should be reported to the IRB within 24 hours. Less serious events must be reported to the IRB within two weeks of their occurrence.

Please complete and sign this form. Submit to the Human Subjects Manager, Mark Long, at Mailstop D-50. Following review by the IRB, the IRB Chair will notify the Deputy ADS, who will notify OPRR in writing of the event and the corrective actions taken.

CDC Investigator: **Protocol Number:** _____

_____ **Participant's I.D. (if available):** _____

Date of Problem/Breach: _____ **Date First Known to You:** _____

Describe in detail the nature of the breach or unanticipated problem and timing of the event (attach addendum if necessary):

Event appears to be:

_____ Directly related _____ Indirectly related _____ Not related to research

Describe impact on participant:

Describe corrective action taken by study investigator: (Check all that apply)

_____ Stop enrollment of new participants
_____ Halt the study
_____ Change data management/ coding procedures
_____ Form committee to review procedures
_____ Other (Please Comment)

Does this event require revision to the (YES or NO):	_____ Protocol	_____ Consent Form

If yes, please submit amendment (CDC form 1252), revised protocol and consent form.

Signature of lead CDC investigator: _____ **Date:** _____

Printed name of lead CDC investigator: _____ Phone: _____

Approvals (Signature and Position Title)	**Date:**	**Remarks:**
Branch Chief:		
Division Director:		
CIO HSC:		

Appendix VI

Protocol Submission Forms

INSTITUTIONAL REVIEW BOARD (IRB)
REQUEST FOR NEW PROTOCOL APPROVAL

Instructions: Use this form when submitting new protocols to the IRB. Please submit this form electronically along with the protocol and any supporting documents to the CIO designated staff official. However, if submitted in hardcopy, please send the original and three copies of all documents to the CIO designated staff official. Consecutively number all pages, beginning with the title page of the protocol, followed by any consent form(s) and ancillary documents. Complete all applicable items or the form will be returned.

Date Submitted by Investigator: _____

PROTOCOL NO. _____ **Date Rec'd HSO** _____
(For Human Subjects Office Use)

Title of Protocol: _____

Proposed Dates for Project - Begin: _____ End: _____

Name of CDC Employee Serving as Principal Investigator (PI) and Degrees:

_____

Scientific Ethics Verification No.: _____ Telephone/FAX No.: _____

CIO/Division/Mailstop: _____ Email Address: _____

Names of Other CDC Employee Co-investigators (use supplemental page if > than 3):

1. _____ *Scientific Ethics* Verification No.: _____
2. _____ *Scientific Ethics* Verification No.: _____
3. _____ *Scientific Ethics* Verification No.: _____

STUDY POPULATION

Estimated Number of Subjects: _____

Gender Distribution:
_____ % Female
_____ % Male

Race/Ethnicity Distribution for Domestic Studies:
_____ % American Indian or Alaskan Native
_____ % Asian or Pacific Islands:
_____ % Black or African American; not of Hispanic Origin
_____ % Hispanic
_____ % White, not of Hispanic Origin

If an international study, provide race/ethnicity of subjects by estimated percentages:

_____

Vulnerable Populations - Do the subjects include: _____ YES _____ NO
If YES, check all that apply:

_____ Pregnant women and/or fetuses as SPECIFIC targets group (Ref: 45 CFR 46, Subpart B)

_____ Prisoners (Ref: 45 CFR 46, Subpart C)

_____ Children 17 years of age or younger (Ref: 45 CFR 46, Subpart D)
_____ If YES, are you requesting a waiver of parental permission?

_____ Mentally disabled

_____ Economically or educationally disadvantaged

STUDY DESIGN ISSUES (check all that apply)

_____ Will CDC investigators have personal identifiers?

_____ Is a waiver or alteration of informed consent being requested in this project? (Ref:45 CFR 46.116)

_____ Is a waiver of documentation of consent being requested for this project? (Ref: 45 CFR 46.117)

_____ If specimens are collected, will they be stored for future use?

_____ Is HIV testing being performed as part of the study?

_____ Is genetic testing planned?

_____ Does the study involve the use of a drug or device? (See FDA Regulations)

_____ If YES, will the study be carried out under an Investigational New Drug (IND) or device (IDE)?

FUNDING (check one)

_____ PGO Funding Mechanism Used:

_____ Cooperative Agreement No(s).: _____

_____ Contract No(s).: _____

_____ Grant: _____

_____ Purchase Order (a.k.a. Simplified Acquisition): _____

_____ Other funding mechanism:

_____ Memorandum of Understanding (MOU) (With whom): _____

_____ Interagency Agreement (IAA) (Name of other agency): _____

_____ Other (Specify type and with whom): _____

_____ Only CDC investigators performing study

_____ Collaborative (Non-CDC Investigators & CDC investigators; no funding involved)

LOCATION OF THIS RESEARCH (Use additional sheets if necessary)

_____ U.S. or its territories? _____ Foreign country (countries)?

List All Collaborating Sites by Full Name and Location (include state):	**OPRR Assurance No.:**
1.	
2.	
3.	
4.	
5.	
6.	
7.	
8.	
9.	
10.	

DATA CONFIDENTIALITY INFORMATION (CIRCLE)				**REFERENCES:**	
Does CDC have an Assurance of Confidentiality to cover this project?	YES	NO	Applied For	N/A	§ 308(d) PHS Act
Does the local site(s) have a Certificate of Confidentiality to cover this project?	YES	NO	Applied For	N/A	§301(d) PHS Act

Approvals (Signature and Position Title): Branch Chief:	**Date:**	**Remarks:**
Division Director:		
CIO Human Subjects Contact:		

INSTITUTIONAL REVIEW BOARD (IRB)
REQUEST FOR CONTINUATION APPROVAL OF PROTOCOL

Instructions: Use this form when submitting protocols for continuing review. Review is required AT LEAST annually; however, the IRB may have determined that your protocol will need to be reviewed more often. Please submit this form electronically along with the current consent form and a copy of the protocol (if changed since last year) and any supporting documents (if changed since last year) to the CIO designated staff official. However, if submitted in hardcopy, please send the original and three copies all documents to the CIO designated official. Consecutively number all pages, beginning with the title page of the protocol (if applicable), followed by any consent form(s) and any applicable ancillary documents. Complete all applicable items or the form will be returned.

Date Submitted by Investigator: _____

PROTOCOL NO. _____ **Date Rec'd HSO** _____

(For Human Subjects Office Use)

Title of Protocol: _____

Proposed Dates for Project - Begin:: _____ End: _____

Name of CDC Employee Serving as Principal Investigator (PI) and Degrees:

_____

Scientific Ethics Verification No.: _____ Telephone/FAX No.: _____
CIO/Division/Mailstop: _____ Email Address: _____

Names of Other CDC Employee Co-investigators (use supplemental page if > than 3):

1. _____ *Scientific Ethics* Verification No.: _____

2. _____ *Scientific Ethics* Verification No.: _____

3. _____ *Scientific Ethics* Verification No.: _____

1. Current Status

_____ Study not yet begun (Provide explanation in item 4. Complete item 6, if applicable)

_____ Active research; contact with subjects continuing (Complete items 2-9)

_____ Active research with subjects completed; study activities involve only data analysis and/or report writing (Complete items 2,5,6,7,9)

_____ Study does not involve contact with subjects (e.g., research using existing records); study activities involve only data analysis and/or report writing (Complete items 5,6,7,9)

2. Study Population

_____ Enrolled this past year

_____ Declined enrollment this past year

_____ Total number of subjects to date

_____ Withdrawn from project this past year

For individuals who were enrolled this year:
Gender distribution:
_____ % Female
_____ % Male

Race/ethnicity distribution of enrolled subjects for domestic studies:

_____ % American Indian or Alaskan Native
_____ % Asian or Pacific Islander
_____ % Black or African American, not of Hispanic origin
_____ % Hispanic
_____ % White, not of Hispanic Origin

If an international study, provide race/ethnicity of subjects by percentages:

_____

Vulnerable Populations - Have any of these populations been added to the study? _____ YES _____ NO
If YES, please check all that apply

_____ Pregnant women (as a SPECIFIC target group)
_____ Fetuses (Ref: 45CFR46, Subpart B)
_____ Prisoners (Ref: 45CFR46, Subpart C)
_____ Children 17 years of age or younger (Ref: 45CFR46, Subpart D)
_____ Mentally disabled
_____ Educationally or economically disadvantaged

3. Collaborating Sites (Use additional sheets if necessary)

3a. List any collaborating sites by name and location (including state) that were added since last continuation approval:

_____ None added

	OPRR Assurance No.:
1.	
2.	
3.	
4.	
5.	
6.	
7.	
8.	

3b. List any collaborating sites by name and location (including state) that were deleted since last continuation approval:

_____ None deleted

1.
2.
3.
4.
5.
6.
7.
8.

4. FUNDING (check one)

_____ PGO Funding Mechanism Used:

_____ Cooperative Agreement No(s).: _____

_____ Contract No(s).: _____

_____ Grant: _____

_____ Purchase Order (a.k.a. Simplified Acquisition):

_____ Other funding mechanism:

_____ Memorandum of Understanding (MOU) (With whom): _____

_____ Interagency Agreement (IAA) (Name of other agency): _____

_____ Other (Specify type and with whom): _____

_____ Only CDC investigators performing study

_____ Collaborative (Non-CDC investigators & CDC investigators; no funding involved)

5. Summary of Activities to Date (Use additional sheets as necessary):

6. Summary of Study Modifications Reviewed and Approved This Past Year (Use additional sheets as necessary):

_____ None

7. Summary of Any New Literature, Findings, or Other Relevant Information (Use addition sheets as necessary):
_____ None

8. **Summary of Adverse Events or Unanticipated Problems** (Use additional sheets as necessary):
_____ None

9. Consent Documents (Attach a copy of each current consent form, telephone consent text, and/or consent letter):

10. Summary of Remaining Activities (Use additional sheets as necessary):

Approvals (Signature and Position Title): Branch Chief:	**Date:**	**Remarks:**
Division Director:		
CIO Human Subjects Contact:		

INSTITUTIONAL REVIEW BOARD (IRB)
REQUEST FOR AMENDMENT APPROVAL OF PROTOCOL

Instructions: Use this form to submit any changes to your research. Please submit this form electronically along with a copy of the protocol, current consent form, and any supporting documents to the CIO designated staff official. However, if submitted in hardcopy, please send the original and three copies of all documents to the CIO designated staff official. Consecutively number all pages, beginning with the title page of the protocol, followed by any consent form(s) and ancillary documents. Complete all applicable items or the form will be returned.

Date Submitted by Investigator: _____

PROTOCOL NO. _____ **Date Rec'd HSO** _____

(For Human Subjects Office Use)

Title of Protocol: _____

Proposed Dates for Project - Begin: _____ End: _____

Name of CDC Employee Serving as Principal Investigator (PI) and Degrees:

_____

Scientific Ethics Verification No.: _____ Telephone/FAX No.: _____

CIO/Division/Mailstop: _____ Email Address: _____

Names of Other CDC Employee Co-investigators (use supplemental page if > than 3):

1. _____ *Scientific Ethics* Verification No.: _____

2. _____ *Scientific Ethics* Verification No.: _____

3. _____ *Scientific Ethics* Verification No.: _____

1. FUNDING (check one)

_____ PGO Funding Mechanism Used:

- _____ Cooperative Agreement No(s).: _____
- _____ Contract No(s).: _____
- _____ Grant: _____
- _____ Purchase Order (a.k.a. Simplified Acquisition): _____

_____ Other funding mechanism:

- _____ Memorandum of Understanding (MOU) (With whom): _____
- _____ Interagency Agreement (IAA) (Name of other agency): _____
- _____ Other (Specify type and with whom): _____

_____ Only CDC investigators performing study

_____ Collaborative (Non-CDC investigators & CDC investigators; no funding involved)

2. Collaborating Sites (Use additional sheets if necessary)

2a. List any collaborating sites by name and location (including state) that were added since last approval:

_____ None added	**OPRR Assurance No.**
1.	
2.	
3.	
4.	
5.	

2b. List any collaborating sites by name and location (including state) that were deleted since last approval:

_____ None deleted

1.

2.

3.

4.

5.

3. Description of proposed modification(s) to the protocol:

4. Reasons for proposed modification(s):

Approvals (Signature and Position Title): Branch Chief:	**Date:**	**Remarks:**
Division Director:		
CIO Human Subjects Contact:		

INSTITUTIONAL REVIEW BOARD (IRB)
REQUEST FOR TERMINATION OF PROTOCOL

Instructions: Use this form when terminating (completed/withdrawn/canceled) a protocol. Please submit this form electronically to the CIO designated staff official. However, if submitted in hardcopy, please send the original and one copy to the CIO designated staff official. Complete all applicable items or the form will be returned.

Date Submitted by Investigator: _____

PROTOCOL NO. _____
Date Rec'd HSO _____
(For Human Subjects Office Use)

Title of Protocol:

_____

Name of CDC Employee Serving as Principal Investigator (PI) and Degrees:

_____

Scientific Ethics Verification No.: _____ Telephone/FAX No.: _____
CIO/Division/Mailstop: _____ Email Address: _____

1. Current status:

_____ CANCELED (Never started) (Attach explanation)
_____ COMPLETED (Complete items 2,3,4)

2. Disposition of Data:

_____ Original data and/or research materials have been destroyed
_____ Linkage between existing data and original source of information has been destroyed. No individuals can be identified from existing data.
_____ Data with identifiers or linkage will be retained. Indicate:

Why:

Where:

How long:

3. Study Population

_____ Enrolled this past year
_____ Declined enrollment this past year
_____ Total number of subjects to date
_____ Withdrawn from project this past year

For individuals who were enrolled this year:
Gender distribution:
_____ % Female
_____ % Male

Race/ethnicity distribution of enrolled subjects for domestic studies:
_____ % American Indian or Alaskan Native
_____ % Asian or Pacific Islander
_____ % Black or African American, not of Hispanic origin
_____ % Hispanic
_____ % White, not of Hispanic Origin

If an international study, provide race/ethnicity of subjects by percentages:

4. Final Report (Attach a copy of the final report for a completed study)

Approvals (Signature and Position Title): Branch Chief:	**Date:**	**Remarks:**
Division Director:		
CIO Human Subjects Contact:		

INSTITUTIONAL REVIEW BOARD (IRB)
RAPID ASSESSMENT REQUEST FOR PROTOCOL APPROVAL

Instructions: Use this form when requesting rapid review of your protocol. Please submit this form electronically and attach, when applicable, a consent form, child's assent form, phone scripts, recruitment fliers, medical records release, and questionnaire (or types of questions, i.e., sensitive/nonsensitive, if an instrument is under development), to the CIO designated staff official. However, if submitted in hardtop, please send the original and seven copies of all documents to the CIO designated staff official. Consecutively number all pages, beginning with the title page of the protocol, followed by any consent form(s) and ancillary documents. Complete all applicable items or the form will be returned.

Date Submitted: _____

PROTOCOL NO. _____ **Date Rec'd HSO** _____

(For Human Subjects Office Use)

Title of Protocol: _____

Name of CDC Employee Serving as Principal Investigator (PI) and Degrees:

_____

Scientific Ethics Verification No.: _____

Work Telephone/FAX No.: _____
Home Telephone/FAX No.: _____

CIO/Division/Mailstop: _____ Email Address: _____

Names of CIO Contact Persons if PI (above) is Not Available (Write in "Same as Above" if applicable): ___

_____

Telephone Nos.:
Work: _____
Home: _____

Email Address: _____

Scientific Ethics Verification No.: _____

Name of CDC Co-PI or Supervisor and Degrees:

_____

Work Telephone No.: _____ Email Address: _____

Work FAX No.: _____ *Scientific Ethics* Verification No.: _____

Study Population

_____ Estimated number of subjects

For individuals who were enrolled this year:
Gender distribution:
_____ % Female
_____ % Male

Race/ethnicity distribution estimate for domestic studies:

_____ % American Indian or Alaskan Native
_____ % Asian or Pacific Islander
_____ % Black or African American, not of Hispanic origin
_____ % Hispanic
_____ % White, not of Hispanic Origin

If an international study, provide race/ethnicity of subjects by estimated percentages:

_____

Vulnerable Populations - Do subjects include: _____ YES _____ NO
If YES, check all that apply

_____ Pregnant women and/or fetuses as a SPECIFIC targets group (Ref: 45CFR46, Subpart B)

_____ Prisoners (Ref: 45CFR46, Subpart C)

_____ Children 17 years of age or younger (Ref: 45CFR46, Subpart D)
_____ If YES, are you requesting a waiver of parental permission?

_____ Mentally disabled

_____ Educationally or economically disadvantaged

STUDY DESIGN ISSUES (check all that apply)

_____ Will CDC investigators have personal identifiers?

_____ Is a waiver or alteration of informed consent being requested in this project? (Ref: 45CFR46.116)

_____ Is a waiver of documentation of consent, being requested for this project? (Ref: 45CFR46.117)

_____ If specimens are collected, will they be stored for future use?

_____ Is HIV testing being performed as part of the study?

_____ Is genetic testing planned?

_____ Is this an outbreak investigation with a research question?

_____ Does the study involve the use of a drug or device in an emergency situation? (See FDA Regulations)
_____ If YES, will the study be carried out under an Investigational New Drug (IND) or device (IDE)?

FUNDING (check one)

_____ PGO Funding Mechanism Used:

_____ Cooperative Agreement No(s).: _____

_____ Contract No(s).: _____

_____ Grant: _____

_____ Purchase Order (a.k.a. Simplified Acquisition): _____

_____ Other funding mechanism:

_____ Memorandum of Understanding (MOU) (With whom): _____

_____ Interagency Agreement (IAA) (Name of other agency): _____

_____ Other (Specify type and with whom): _____

_____ Only CDC investigators performing study

_____ Collaborative (Non-CDC investigators & CDC investigators; no funding involved)

LOCATION OF THIS RESEARCH (Use additional sheets if necessary)

_____ U.S. or its territories? _____ Foreign country (countries)?

List All Collaborating Sites by Full Name and Location (include state):	**OPRR Assurance No.**
1.	
2.	
3.	
4.	
5.	

DATA CONFIDENTIALITY INFORMATION **REFERENCES:**

Does CDC have an Assurance of Confidentiality to cover this project?	YES	NO	Applied For	N/A	§ 308(d) PHS Act
Does the local site(s) have a Certificate of Confidentiality to cover this project?	YES	NO	Applied For	N/A	§301(d) PHS Act

Summary of the public health problem that the project will address:

Research question for this project:

Objectives for this research:

Setting(s) for, and the circumstances of, participant recruiting:

Summary of the procedures of this research and their degree of risk:

Risk of the research (physical, psychological, social):

Benefits for study participants:

Information handling (i.e., security and confidentiality) and specimen handling:

Reasons and details, if consent needs to be waived or altered (otherwise, write "Not Applicable" in the space below:

Details of identity linkage and the feedback of results, if samples are being stored (otherwise, write "Not Applicable" in the space below):

Approvals (Signature and Position Title): Branch Chief:	**Date:**	**Remarks:**
Division Director:		
CIO Human Subjects Contact:		

HUMAN SUBJECTS OFFICE (HSO)
DOCUMENTATION OF EXEMPTION DETERMINATION FOR PROTOCOL

Instructions: Use this form when submitting a request for exemption from 45 CFR 46. Please submit this form electronically along with the protocol (or project description) and any supporting documents to the CIO designated staff official. However, if submitted in hardcopy, please send the original to the Human Subjects Office through the CIO designated staff official. Consecutively number all pages, beginning with the title page of the protocol, followed by any consent form(s) and ancillary documents. Complete all applicable items or the form will be returned.

Date Submitted by Investigator: _____

PROTOCOL NO. _____ **Date Rec'd HSO** _____

(For Human Subjects Office Use)

Title of Protocol: _____

Proposed Dates for Project - Begin: _____ End: _____

Name of CDC Employee Serving as Principal Investigator (PI) and Degrees:

_____

Scientific Ethics Verification No.: _____ Telephone/FAX No.: _____

CIO/Division/Mailstop: _____ Email Address: _____

Names of Other CDC Employee Co-investigators (use supplemental page if > than 3):

1. _____ *Scientific Ethics* Verification No.: _____
2. _____ *Scientific Ethics* Verification No.: _____
3. _____ *Scientific Ethics* Verification No.: _____

STUDY POPULATION

Estimated Number of Subjects: _____

Gender distribution:
_____ % Female:
_____ % Male:

Race/Ethnicity distribution for domestic studies:
_____ % American Indian or Alaskan Native
_____ % Asian or Pacific Islander
_____ % Black or African American; not of Hispanic Origin
_____ % Hispanic
_____ % White, not of Hispanic Origin

If an international study, provide race/ethnicity of subjects by estimated percentages:

_____

FUNDING (check one)

_____ PGO Funding Mechanism Used:

_____ Cooperative Agreement No(s).: _____

_____ Contract No(s).: _____

_____ Grant: _____

_____ Purchase Order (a.k.a. Simplified Acquisition): _____

_____ Other funding mechanism:

_____ Memorandum of Understanding (MOU) (with whom): _____

_____ Interagency Agreement (IAA) (name of other agency): _____

_____ Other (specify type and with whom): _____

_____ Only CDC investigators performing study

_____ Collaborative (Non-CDC Investigators & CDC investigators; no funding involved)

LOCATION OF THIS RESEARCH (Use additional sheets if necessary)

_____ U.S. or its territories? _____ Foreign country (countries)?

List All Collaborating Sites by Full Name and Location (include state):	**OPRR Assurance No.:**
1.	
2.	
3.	
4.	
5.	

The Federal Regulations, under §46.101, establish categories of research that are exempt from the requirements set forth in 45 CFR 46. To determine whether the proposed research is exempt under one of these categories, please COMPLETE EACH SECTION BELOW.

Does the proposed research involve prisoners?

YES _____ This research cannot be exempted under any category listed below. All research involving prisoners must be reviewed by an IRB.

NO _____

Does the proposed research involve fetuses, pregnant women, or human in vitro fertilization as TARGETS (such that Subpart B would apply)?

YES _____ This research cannot be exempted under any category listed below. All research involving fetuses, pregnant women, or human in vitro fertilization must be reviewed by an IRB.

NO _____

1. <u>Educational Research</u>: Is this research conducted in established or commonly accepted education settings, AND does the research involve normal educational practices (e.g., research on regular and special education strategies or research on the effectiveness of, or comparison among, instructional techniques, curricula or classroom management methods) ?

YES _____

NO _____

2. <u>Research Involving Surveys, Interview Procedures (including Focus Groups), Observations of Public Behavior, or Educational Tests:</u> Will this research use educational tests (i.e., cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior?

YES _____

NO _____

2.1 Will children (17 years of age or younger) be research subjects?

YES _____ IRB review is required unless exempt under § 46.101 (b)
NO _____

2.2 Is the information recorded in such a manner that human subjects can be identified <u>directly or indirectly</u> through identifiers (such as a code) linked to the subjects?

YES _____

NO _____

2.3 Will any disclosure of the human subjects' responses outside of the research setting have the potential to place the subjects at risk of criminal or civil liability, or be damaging to the subjects' financial standing, employability or reputation? (Examples here include: the collection of sensitive data regarding the subjects' (or relatives' or associates') possible substance abuse, sexuality, criminal history or intent, medical or psychological condition, financial status, or similarly compromising information).

YES _____

NO _____

2.4 Are the human subjects elected or appointed public officials or candidates for public office?

YES _____

NO _____

2.5 Does federal statute(s) require(s), without exception, that confidentiality of the personally identifiable information will be maintain throughout the research and thereafter? (Note: CDC can use this exemption criterion only in the case where a 308(d) Assurance of Confidentiality has been obtained to cover the research).

YES _____

NO _____

3. <u>Existing Data Which Is Publicly Available or Unidentifiable:</u> Does this research involve the collection or study of existing* data, documents, records, pathological or diagnostic specimens? (*"existing" means the data were available before the study begins.)

YES _____

NO _____ Skip to 4

3.1 Is this material or information publicly available?

YES _____

NO _____

3.2 Is this material or information recorded in such a manner by the investigator that the subjects cannot be identified <u>directly or indirectly</u> through identifiers linked to the subjects? (Note: If a link is created by an investigator, even temporarily, for research purposes, this criterion is not met. If a temporary link is created by clinical staff who already have access to the data, this criterion is met.)

YES _____, there is no identifying information and no unique identifiers or codes.

NO _____, there are identifiers (including codes).

4. <u>Public Benefit or Service Programs</u>: (Note: At the present time, CDC does not have authority to use this exemption category; however if you think your research would qualify, please discuss with the Human Subjects Office).

Is this research or demonstration project conducted under the approval of the Secretary of DHHS and designed to study, evaluate, or examine:

1. **Public benefit or services programs,**
2. **Procedures for obtaining benefits or services under these programs,**
3. **Possible changes in or alternatives to these programs, or**
4. **Possible changes in methods or levels of payments for benefits or services under these programs ?**

YES _____

NO _____

5. <u>Food Research:</u> Is this a taste or food evaluation or a consumer taste or food acceptance study?

YES _____

NO _____

5.1 Will only wholesome foods without additives be consumed OR will any food ingredients (including additives) consumed be demonstrably at or below the level, and for a use found to be safe, or agricultural chemical or environmental contaminants demonstrably at or below the level found to be safe, by the Food and Drug Administration or approved by the Environment Protection Agency or the USDA Food Safety and Inspection Service?

YES _____

NO _____

Please attach a brief (1-2 pages) description (should include research questions, study population, design and methods in sufficient detail to make a determination about exemption status) or protocol (if available) for the research study. Please include an explanation of why this project is exempt.

Approvals (Signature and Position Title): Branch Chief:	**Date:**	**Remarks:**
Division Director:		
CIO Human Subjects Contact:		

References

The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. 1979.

Inclusion of Women and Ethnic Minorities in Research. CDC Manual Guide-- General Administration No. 80. Centers for Disease Control and Prevention. 1996.

Policy on Informing Those Tested about HIV Serostatus. United States Public Health Service. 1988.

Protecting Human Research Subjects: Institutional Review Board Guidebook. Office for Protection from Research Risk, National Institutes of Health. 1993.

Protection of Human Research Subjects. Title 45 Code of Federal Regulations Part 46 (45 CFR 46). Department of Health and Human Services. 1996.

Protection of Human Subjects Title 21 Code of Federal Regulations Part 50 (21 CFR 50). Food and Drug Administration. 1995.

Institutional Review Boards Title 21 Code of Federal Regulations Part 56 (21 CFR 56). United States Food and Drug Administration. 1995.

Investigational Drugs Title 21 Code of Federal Regulations Part 312 (21 CFR 312). Food and Drug Administration. 1995.

Investigational Devices Title 21 Code of Federal Regulations Part 812 (21 CFR 812). Food and Drug Administration. 1995.

Information Sheets: Guidance for Institutional Review Boards and Clinical Investigators **Food and Drug Administration Office of Health Affairs. Department of Health and Human Services. 1998.**